Ömer Faruk Turan
Uludağ Ü.Tıp F.Nöroloji Anabilim Dalı. 15 Şubat 2019 Ankara

MULTİPL SKLEROZ'DA ORAL TEDAVİLER

Oral tedaviler

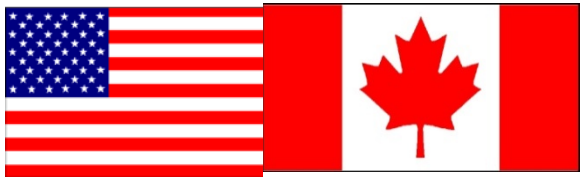
- Dimetil Fumarat
- Fingolimod
- Teriflunomid
- Kladribine

Dimetil Fumarat

Tecfidera 'ya onay

→ T.C. SAĞLIK BAKANLIĞI / THE MINISTRY OF HEALTH OF TURKEY →

Aralık 2016



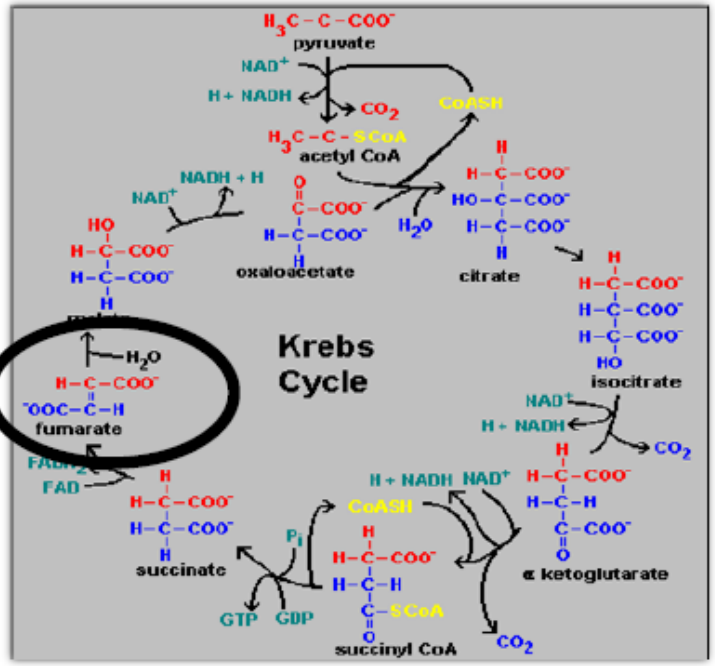
→ DEPARTMENT OF HEALTH & HUMAN SERVICES • USA FDA →

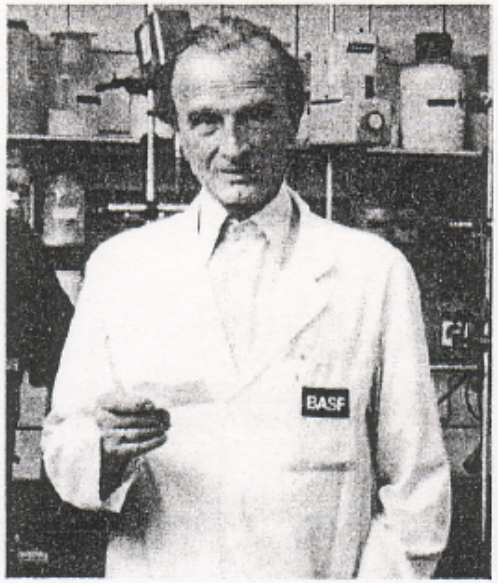
Mart, 2013

→ EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH →

Mart, 2013

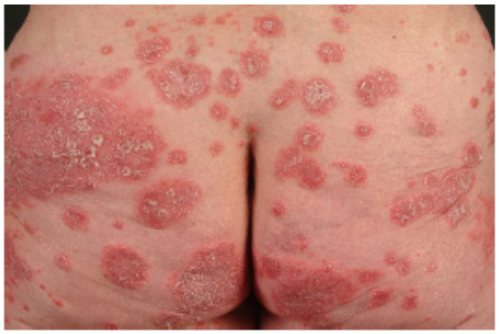
Fumaric acid esters (FAE): Dermatology

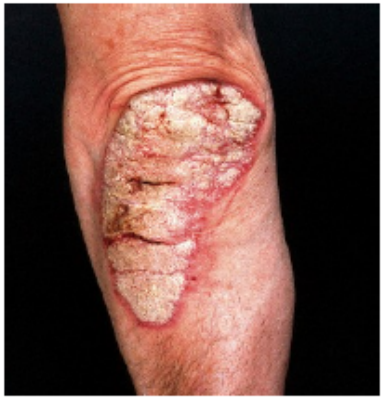




privat

Dr. Walter Schweckendiek





- FAE: self medication in psoriasis (Schweckendiek)
- Fumaderm® psoriasis approval 1994: > 185.000 patient years
- BG12 for MS: further development (DMF, galenics)

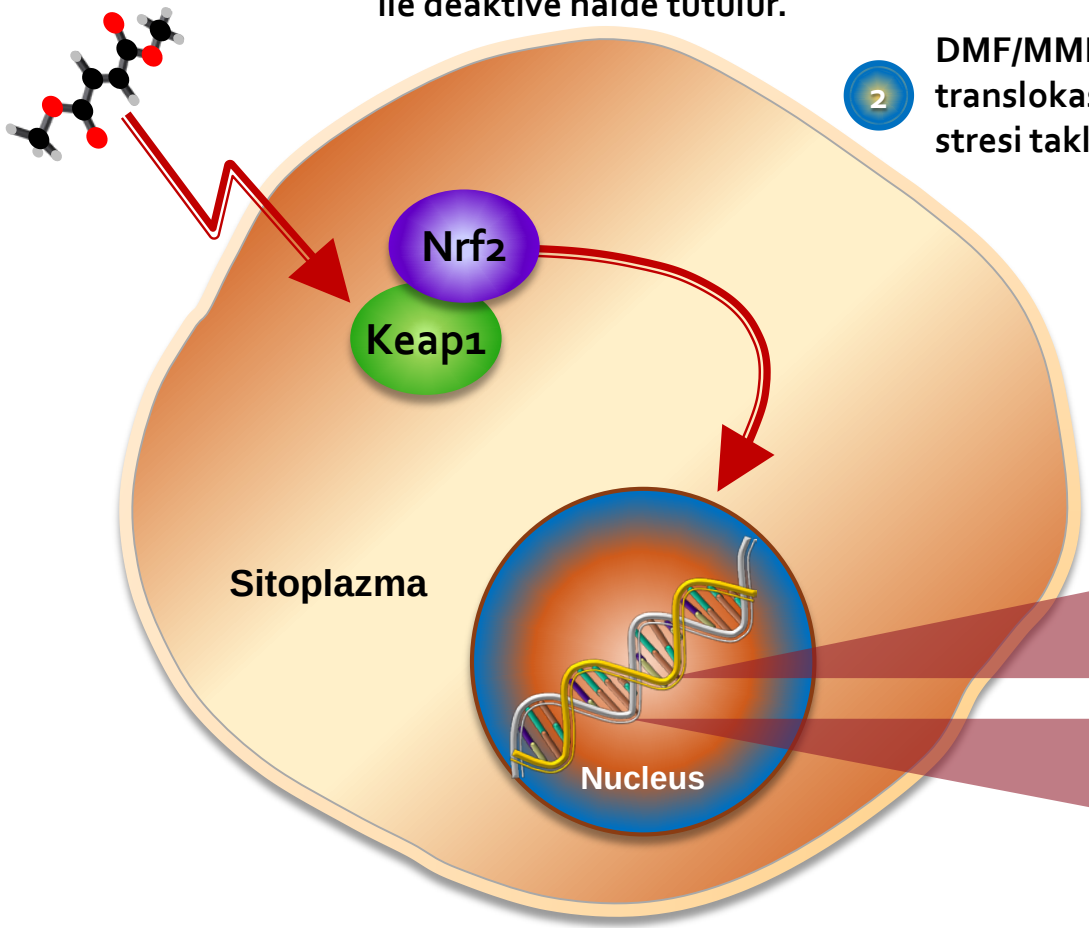
Dimetil Fumarat ve Monometil Fumarat, Nrf2 yolağının aktivasyonu ile Antioksidan ve Antiinflamatuar yanıtları aktive eder.

DMF/MMF

1 sitoplazmada Keap1[1] vasıtası ile deaktive halde tutulur.

2 DMF/MMF, Nrf2'nin nukleusa translokasyonuna sebep olur (fizyolojik stresi taklit ederek)[2]

3 Nrf2, yerel savunma mekanizmalarını aktive eder.[1,3]



Antioksidan yanıt

Inflamatuar yanıt

Nrf2=nuclear factor (erythroid-derived 2)-like 2; Keap1=kelch-like ECH-associated protein.

van Horssen J et al. *Biochem Biophys Acta.* 2011;1812:141-150; Linker RA et al. *Brain.* 2011;134:679-692; Scannevin R et al. *J Pharmacol Exp Ther.* 2012;341:274-284.

Fumarate

J Neurol (2013) 260:2286–2296
DOI 10.1007/s00415-013-6968-1

ORIGINAL COMMUNICATION

Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing–remitting multiple sclerosis: subgroup analyses of the CONFIRM study

Michael Hutchinson · Robert J. Fox · David H. Miller · J. Theodore Phillips · Mariko Kita · Eva Havrdova · John O'Gorman · Ray Zhang · Mark Novas · Vissia Viglietta · Katherine T. Dawson

J Neurol (2013) 260:2297–2305
DOI 10.1007/s00415-013-6954-7

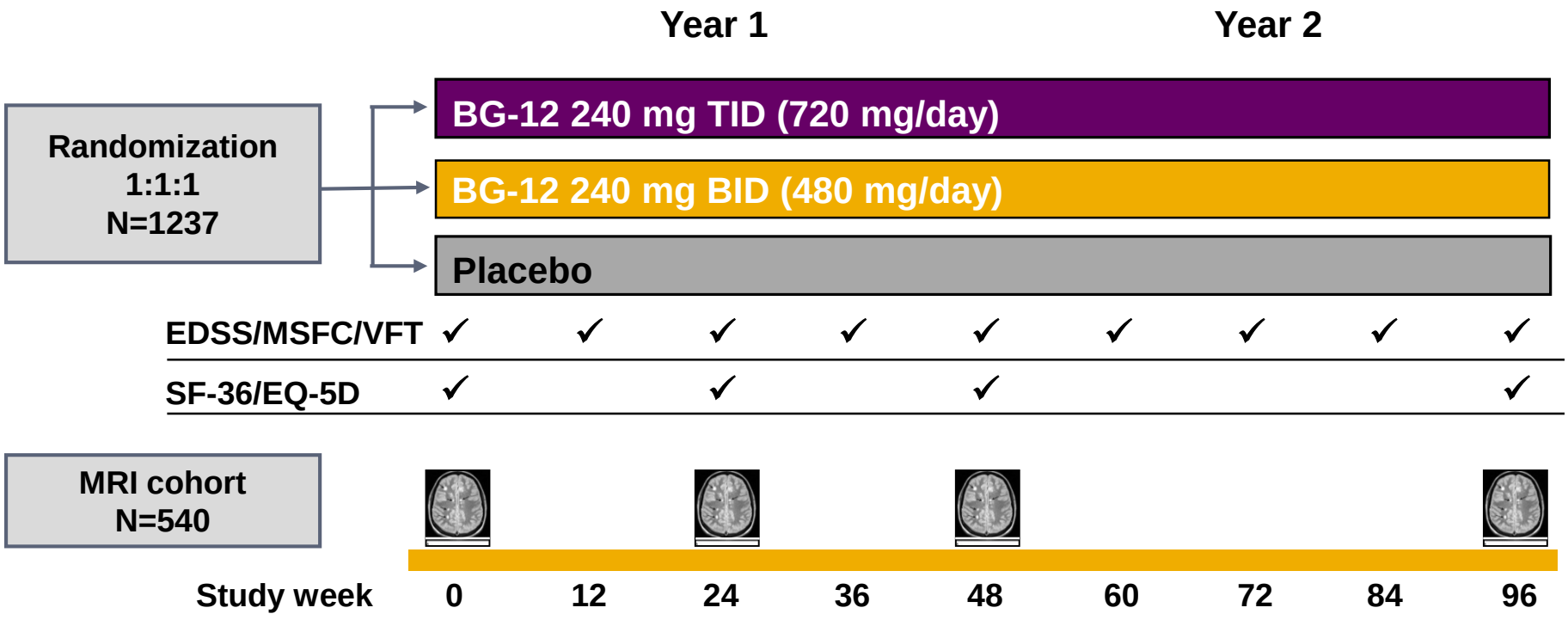
ORIGINAL COMMUNICATION

Clinical efficacy of BG-12 (dimethyl fumarate) in patients with relapsing–remitting multiple sclerosis: subgroup analyses of the DEFINE study

Amit Bar-Or · Ralf Gold · Ludwig Kappos · Douglas L. Arnold · Gavin Giovannoni · Krzysztof Selmaj · John O'Gorman · Monica Stephan · Katherine T. Dawson

Received: 20 February 2013 / Revised: 2 May 2013 / Accepted: 3 May 2013 / Published online: 25 June 2013

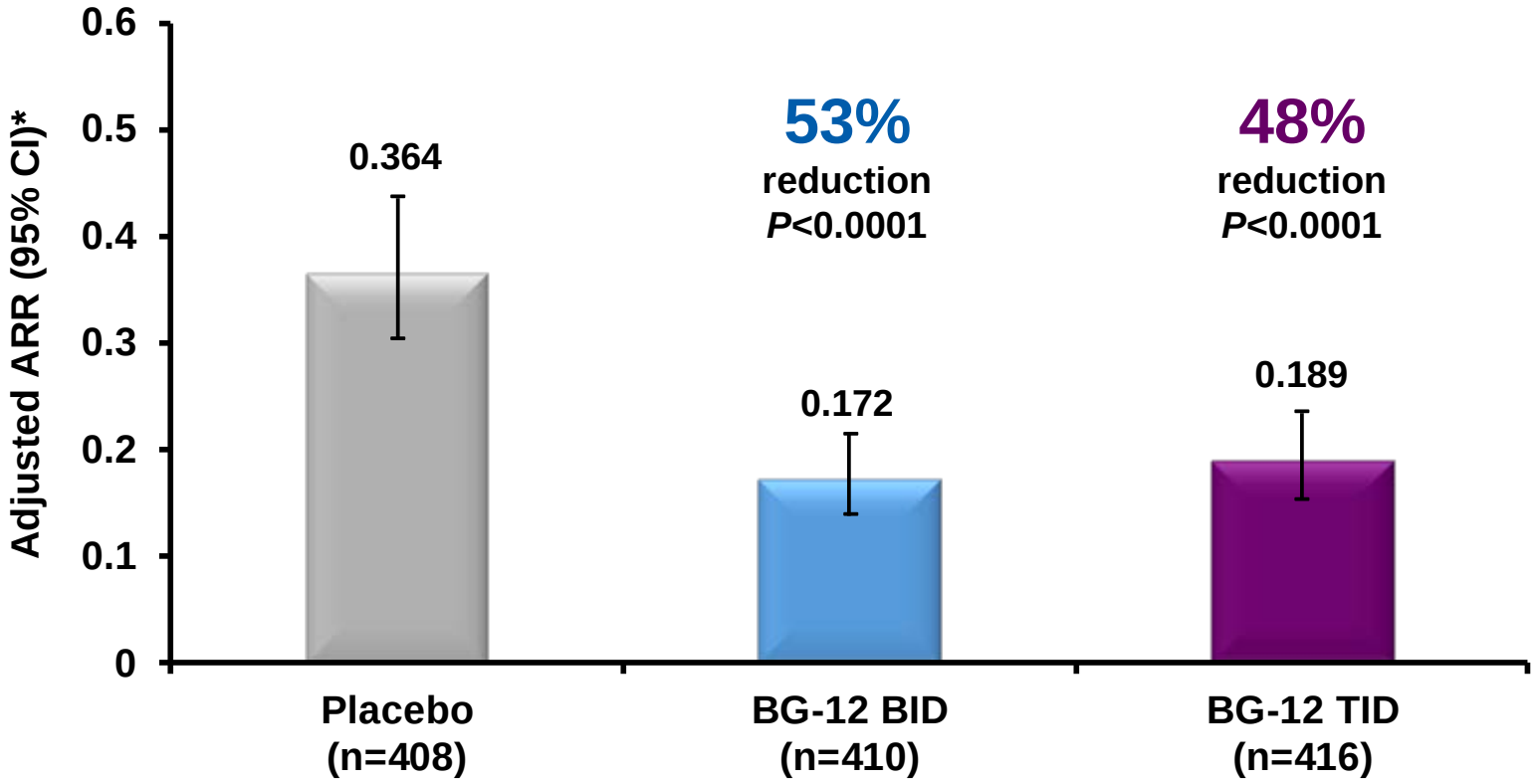
DEFINE: Çalışma Dizaynı



	0	12	24	36	48	60	72	84	96
Blood chemistry/urinalysis Vital signs/pregnancy test	✓	✓ ✓ ✓	✓ ✓ ✓	✓ ✓ ✓	✓ ✓ ✓	✓ ✓ ✓	✓ ✓ ✓	✓ ✓ ✓	✓ ✓ ✓
Microglobulin/microalbumin	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hematology	✓	✓ ✓ ✓	✓	✓	✓	✓	✓	✓	✓

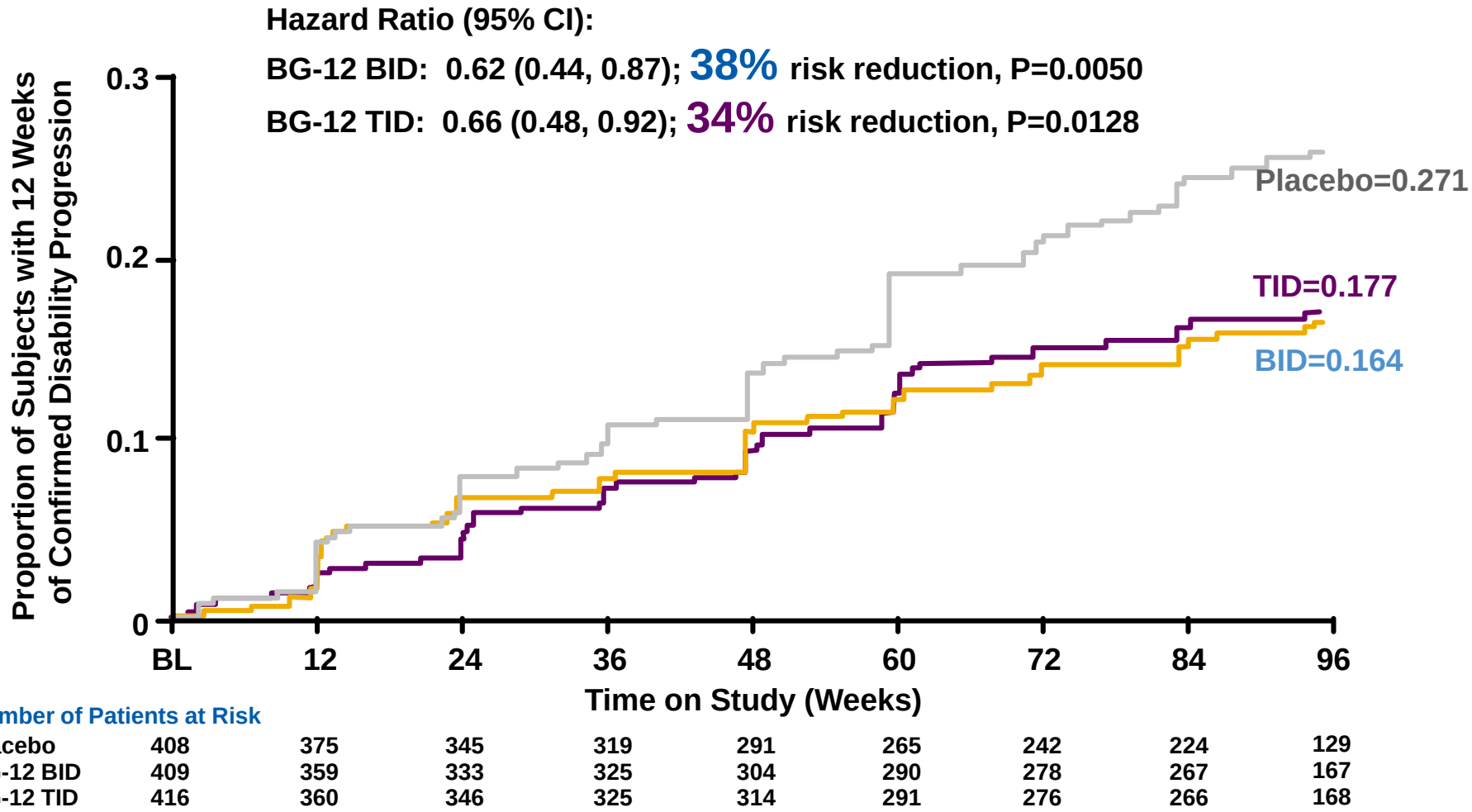
Less frequently: lipid profile, physician exam. As needed: urine cytology.

DEFINE:Yıllık Atak oranı (ARR) – 2 Yıllık (Sekonder Sonlanım Noktası)



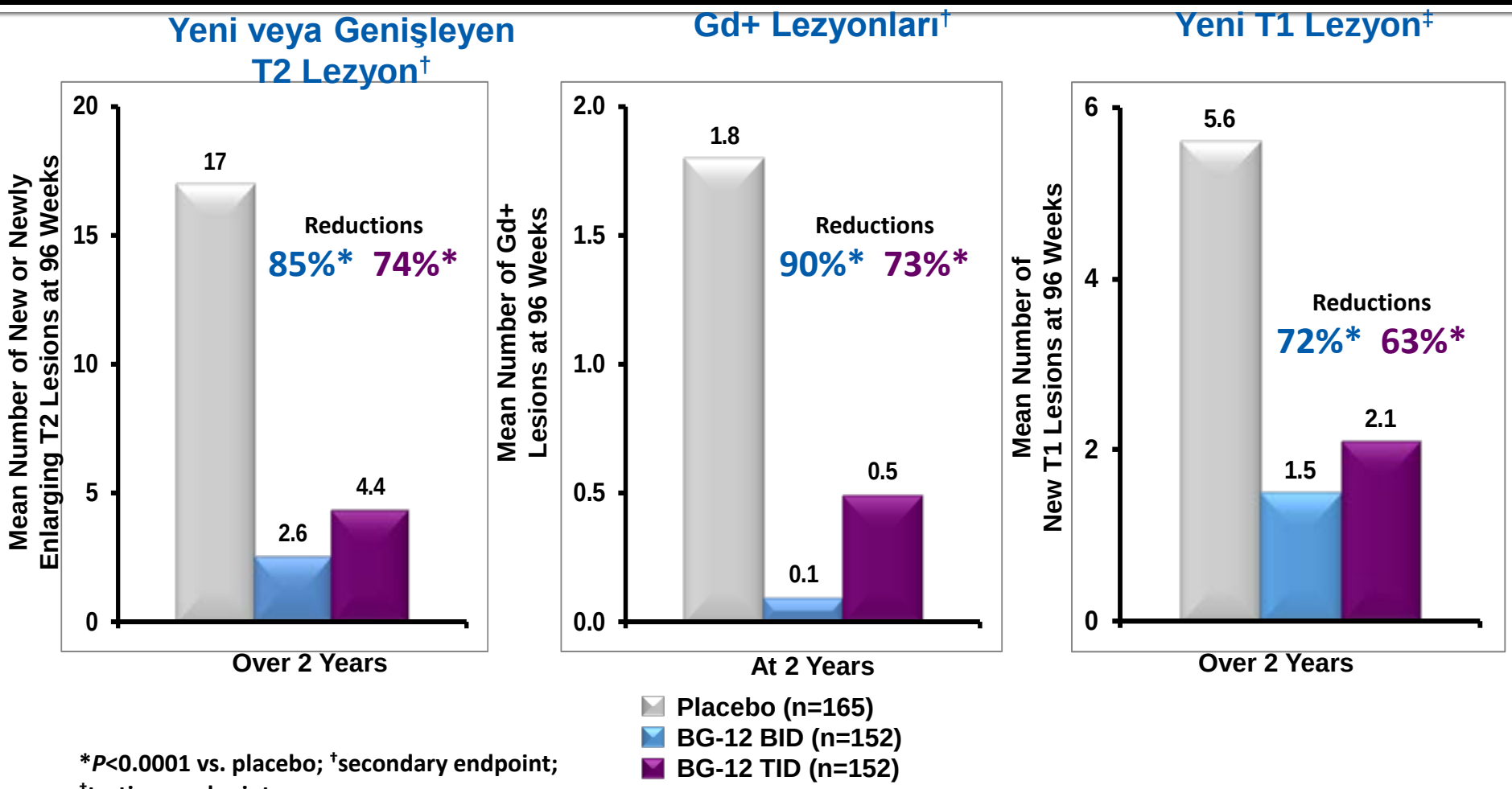
*ARR calculated with negative binomial regression, adjusted for baseline EDSS score (≤2.0 vs >2.0), baseline age (<40 vs ≥40 years), region, and number of relapses in the 1 year prior to study entry.

DEFINE:12-Hafta Dizabilite Progresyonu (Sekonder Sonlanım Noktası)



Patients were censored if they withdrew from study or switched to alternative MS medication without a progression.

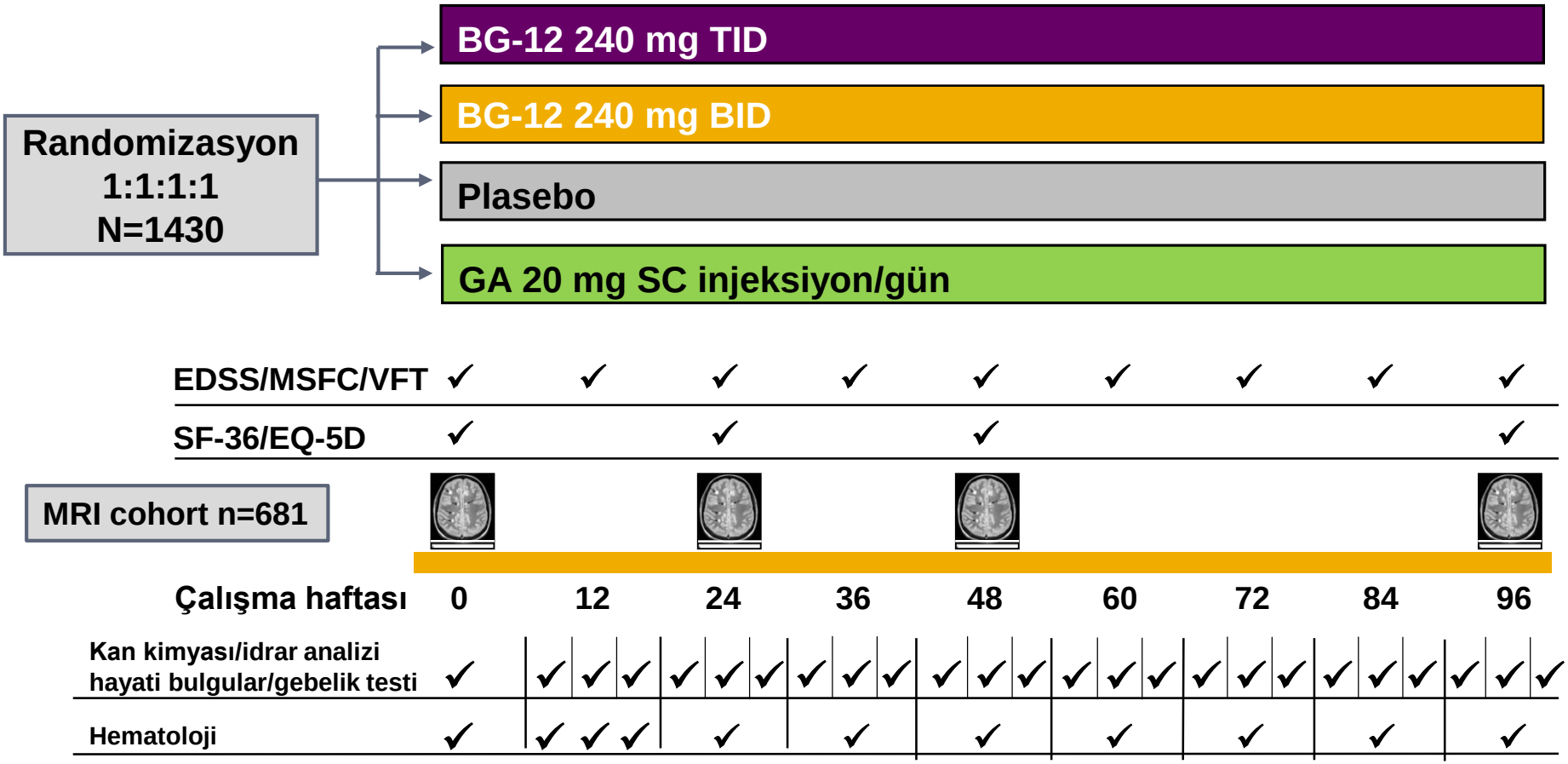
DEFINE: MRG Sonuçları



*P<0.0001 vs. placebo; †secondary endpoint; ‡tertiary endpoint.

Presented at ECTRIMS; October 19–22, 2011; Amsterdam, The Netherlands. Poster 831.

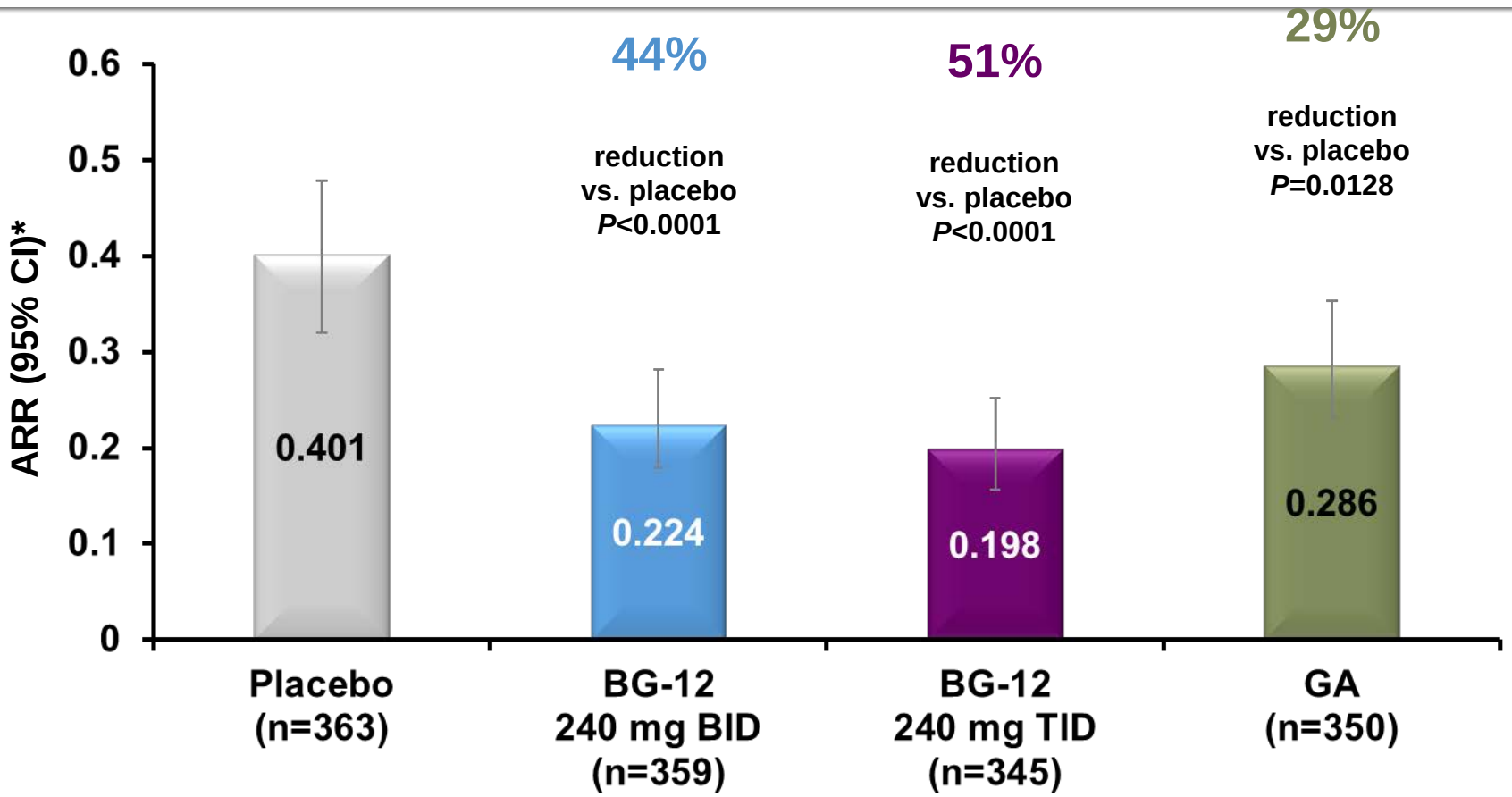
CONFIRM Çalışma Dizaynı



Daha düşük sıklıkla: lipid profili, fizik muayene. İhtiyaç durumunda: idrar sitolojisi.

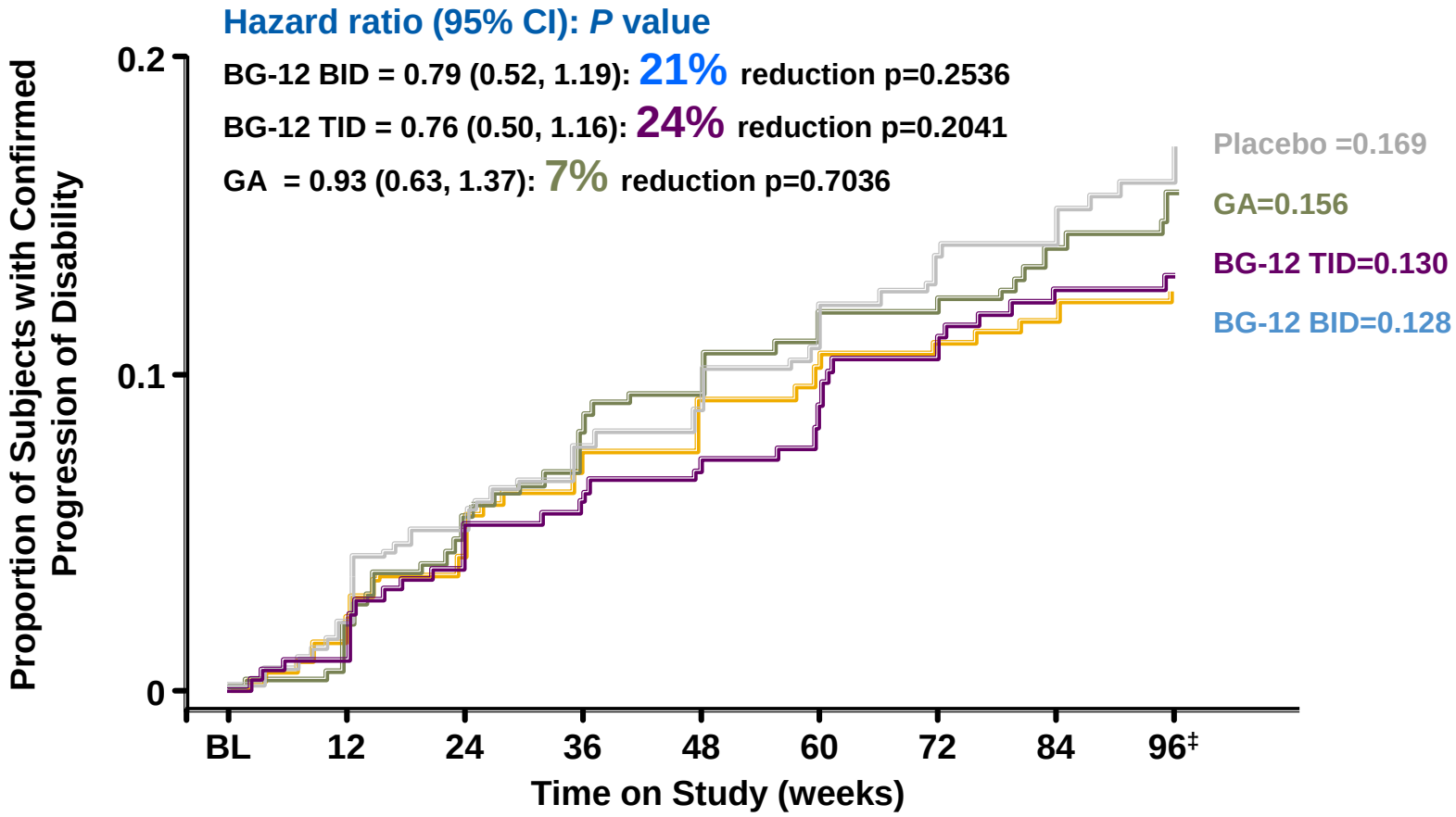
CONFIRM: Yıllık Atak Oranı (ARR)

(Primer sonlanım noktası)



*ARR calculated with negative binomial regression, adjusted for baseline EDSS score (≤2.0 vs >2.0), baseline age (<40 vs ≥40 years), region, and number of relapses in the year prior to study entry.

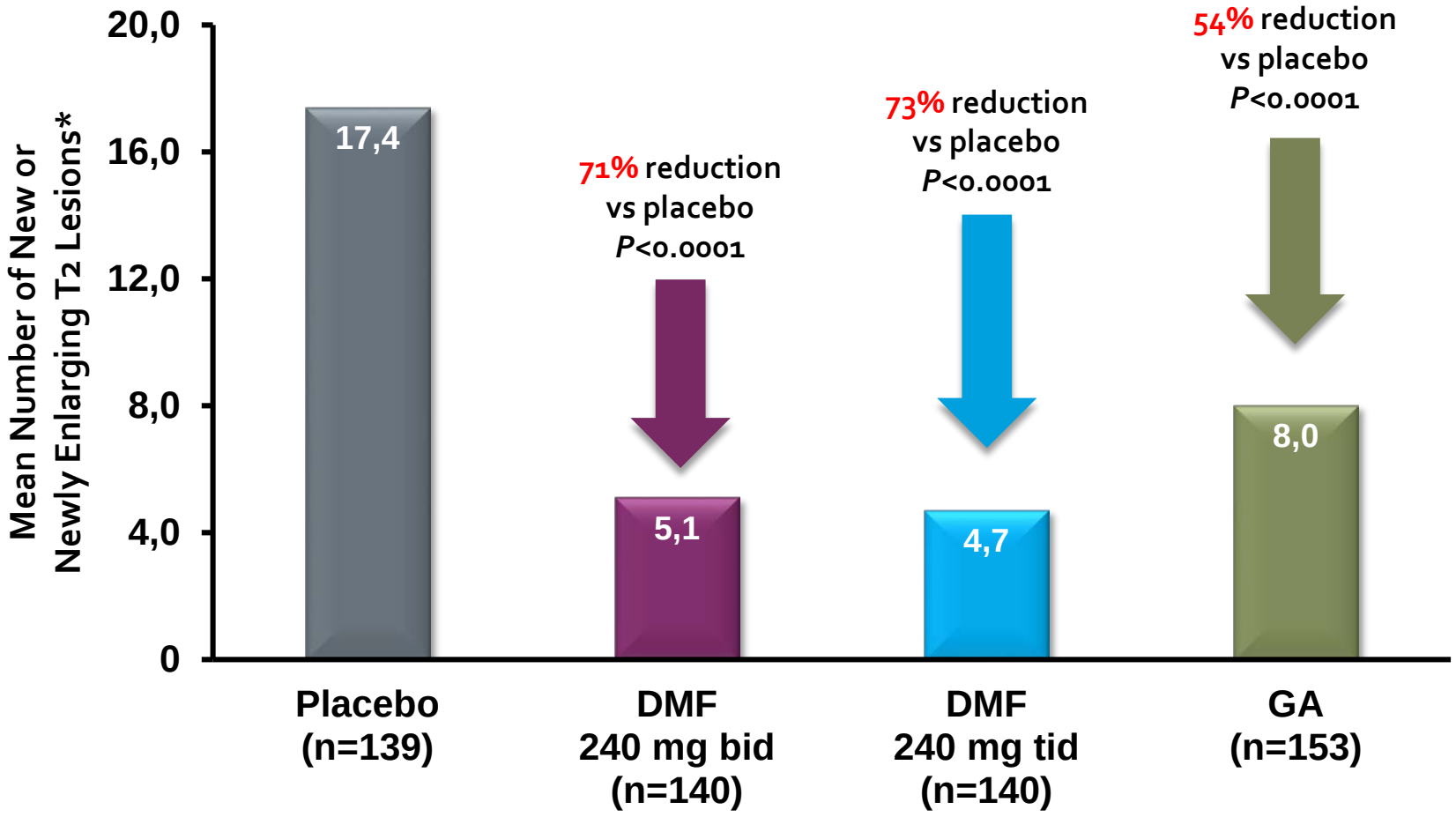
12-Hafta Dizabilite Progresyonu
(Sekonder Sonlanım Noktası)



Patients at Risk									
240 mg BID	363	339	317	297	273	254	235	228	205*
240 mg TID	359	323	302	283	270	263	257	249	220*
GA	345	309	287	277	269	262	249	238	222*
	350	326	307	291	279	269	262	249	231*

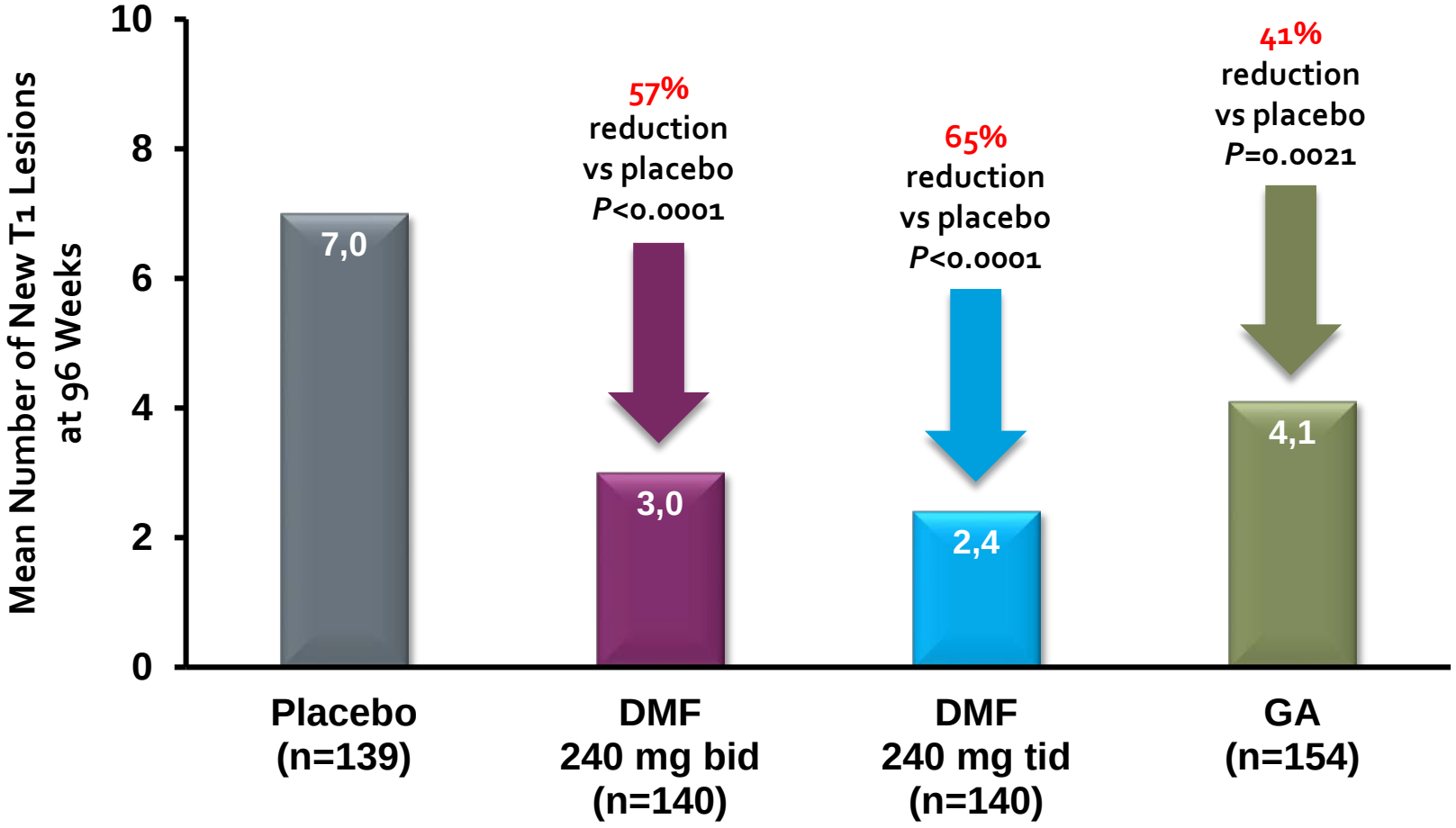
*Numbers at risk 5 days prior to Week 96 (earlier window of Week 96 visit).

CONFIRM: Yeni veya Genişleyen T2 Lezyon sayısı-2 Yılda



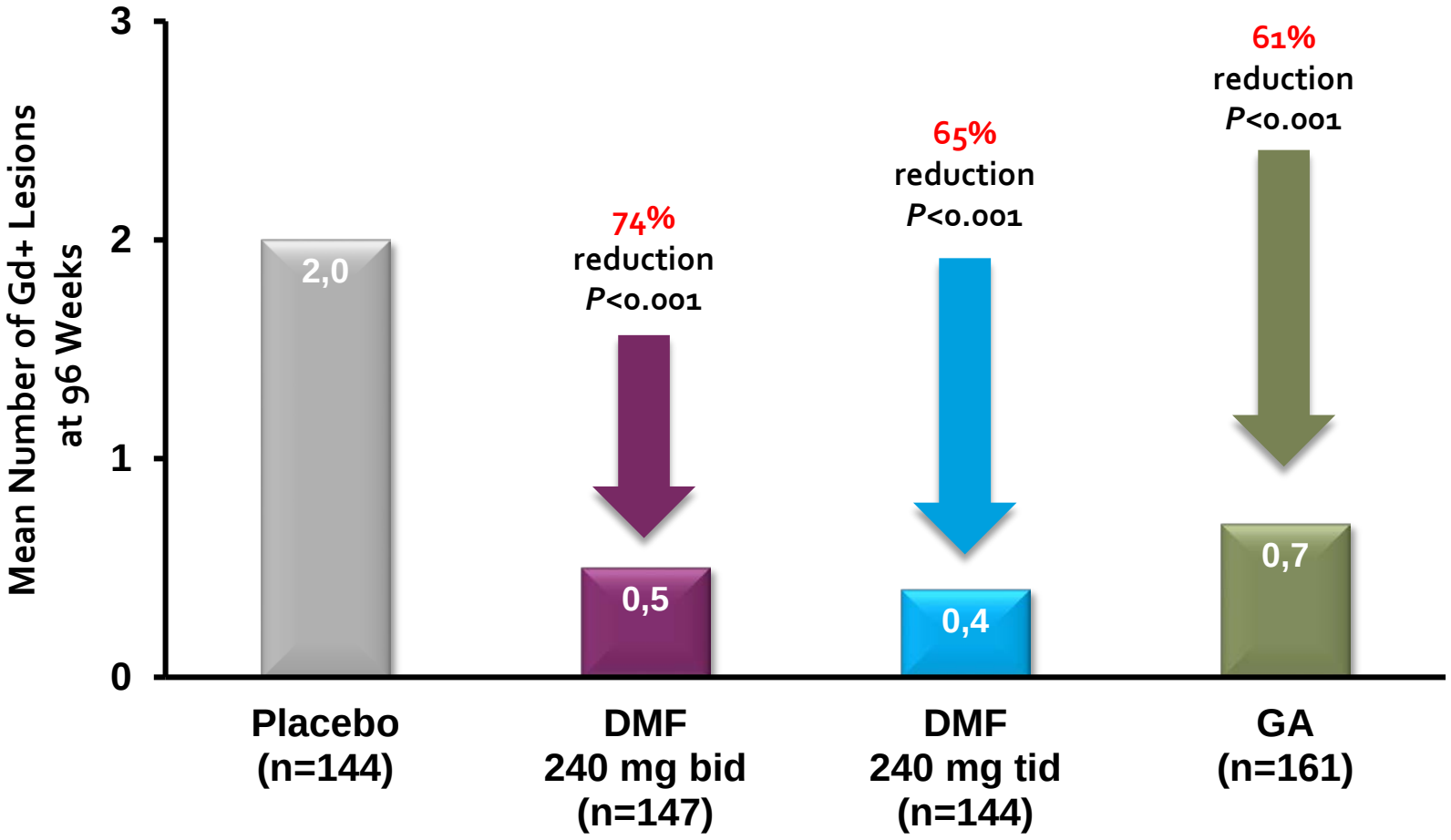
*Negative binomial regression was used for the analysis adjusted for region and baseline T2 lesion volume.
Fox R et al. Presented at AAN; April 21–28, 2012; New Orleans, LA. S01.003;
Miller D et al. Presented at AAN; April 21–28, 2012; New Orleans, LA. S11.001.

CONFIRM: Yeni ortalama T1- Hipointense Lezyon Sayısı- 2 Yılda



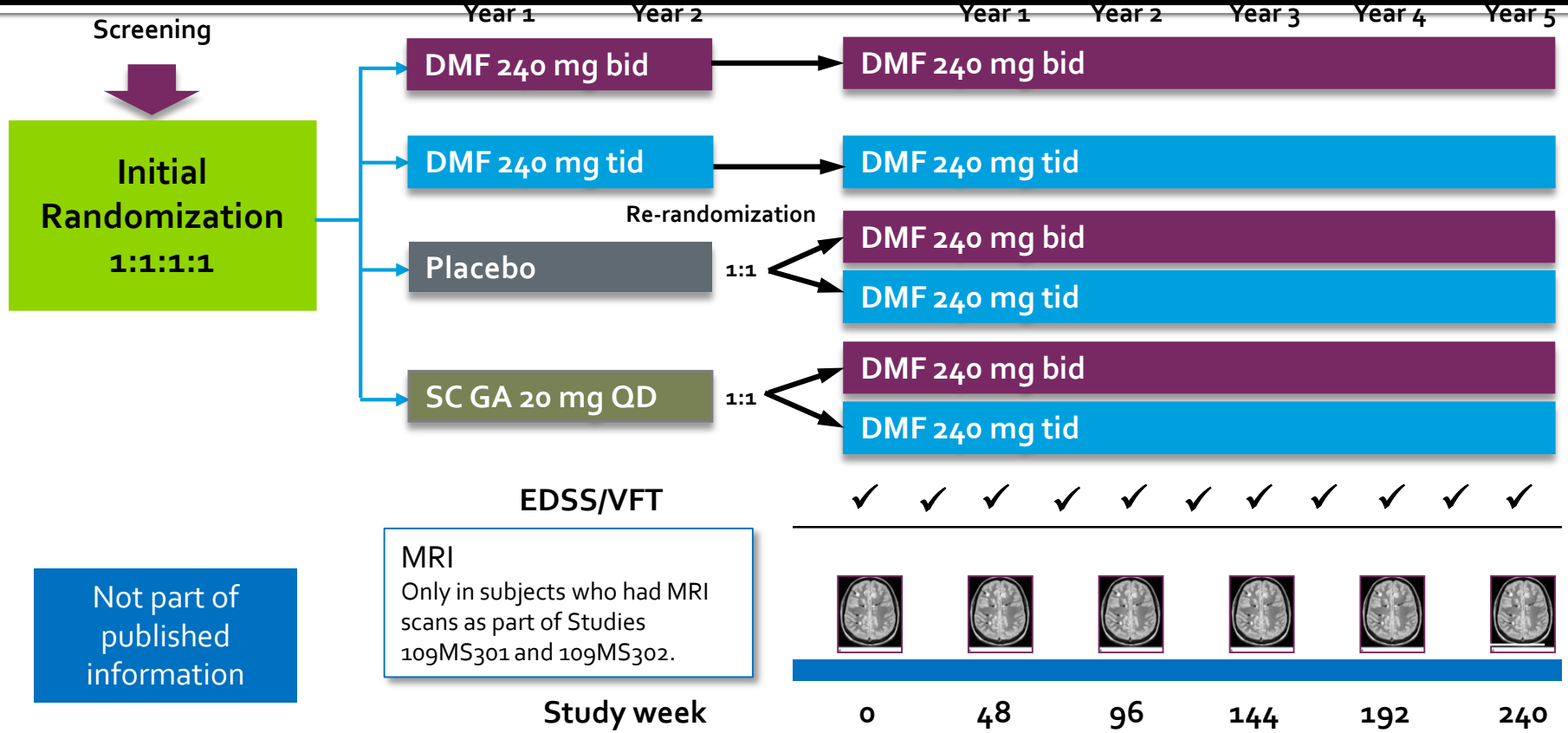
Observed data after switch to alternative MS therapy were excluded; data were adjusted for region and baseline volume of lesions.
Miller D et al. Presented at AAN; April 21–28, 2012; New Orleans, LA. S11.001.

CONFIRM: Gd+ Lezyon- 2 Yılda



Fox R et al. *N Engl J Med*. 2012;367:1087-1197 (supplementary appendix)..

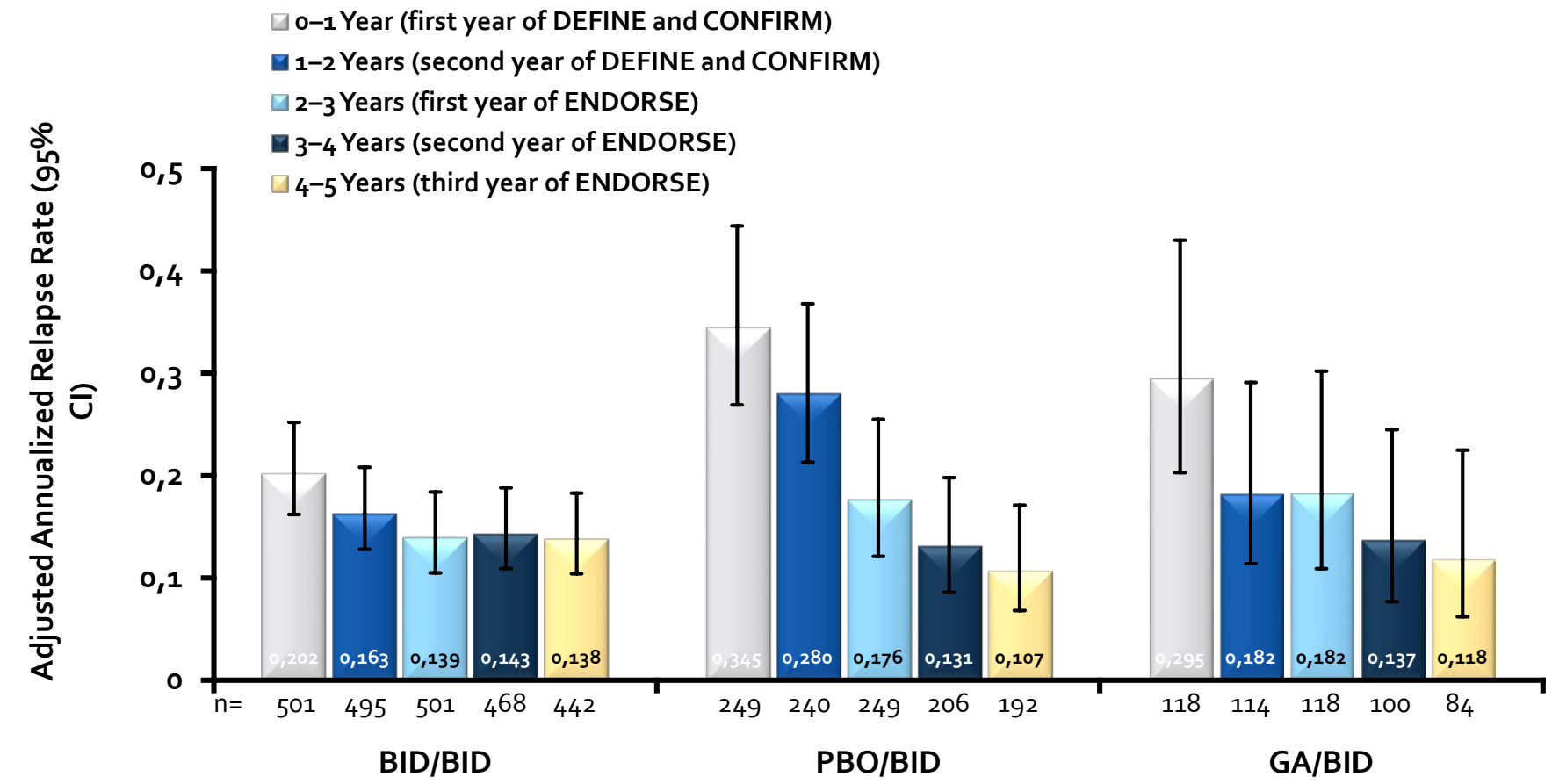
ENDORSE: Çalışma Dizaynı



Laboratory assessments:
Blood chemistry and urinalysis at baseline, then every 4 weeks until week 24, and every 12 weeks thereafter.
Hematology laboratory parameters at baseline and every 12 weeks thereafter.

VFT=visual function test.
Biogen Idec, data on file.

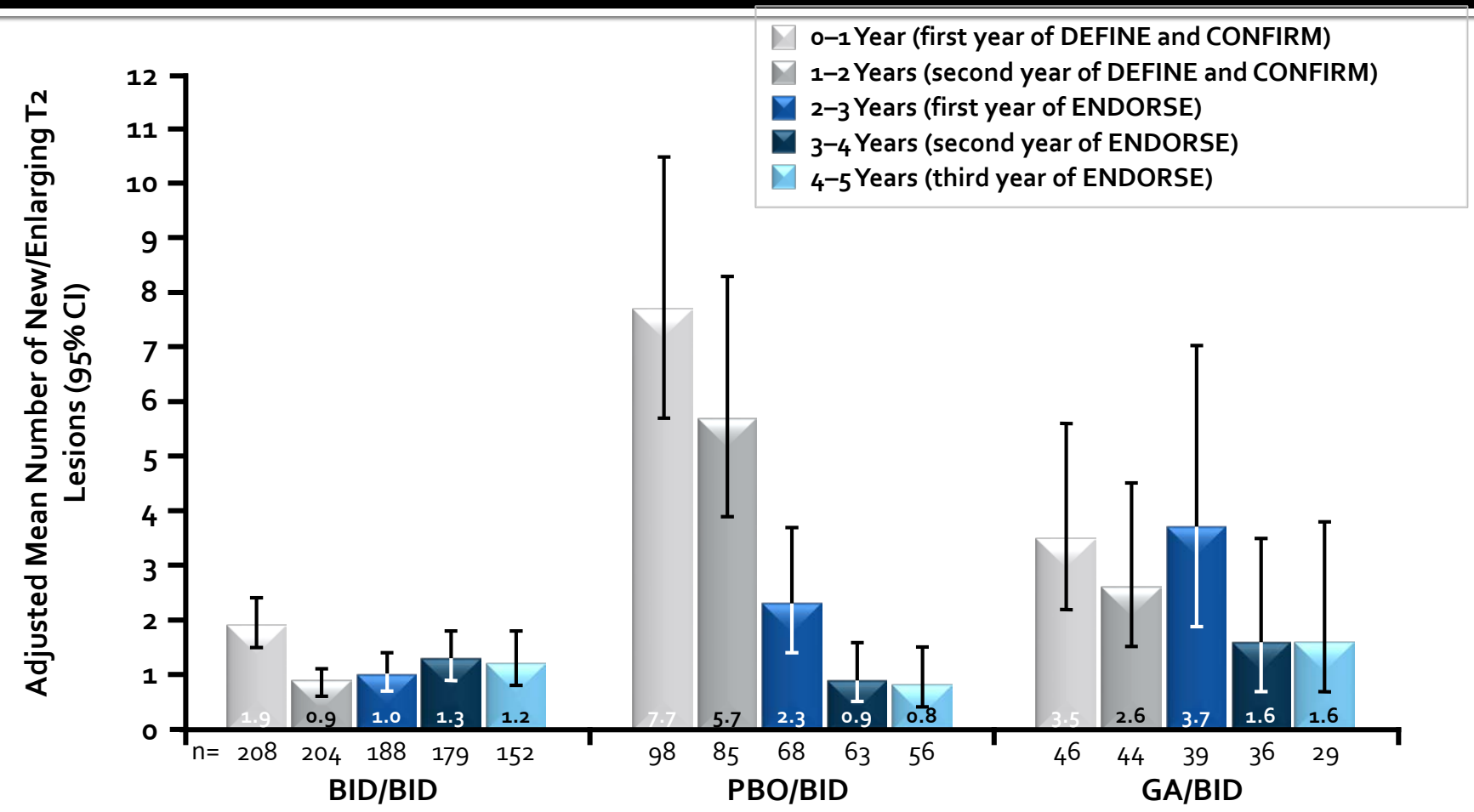
ENDORSE Klinik Etkinlik: Yıllara göre Yıllık Atak Oranı



Adjusted annualized relapse rate and 95% confidence interval (CI) based on negative binomial Poisson regression, adjusted for baseline EDSS score (≤2.0 vs >2.0), baseline age (<40 vs ≥40 years), region, and number of relapses in the 1 year prior to entry into DEFINE or CONFIRM. Data after subjects switched to alternative multiple sclerosis medications during the period are excluded. PBO=placebo.

Gold R et al. Presented at ACTRIMS-ECTRIMS; 10–13 September 2014; Boston, MA, USA. P110.

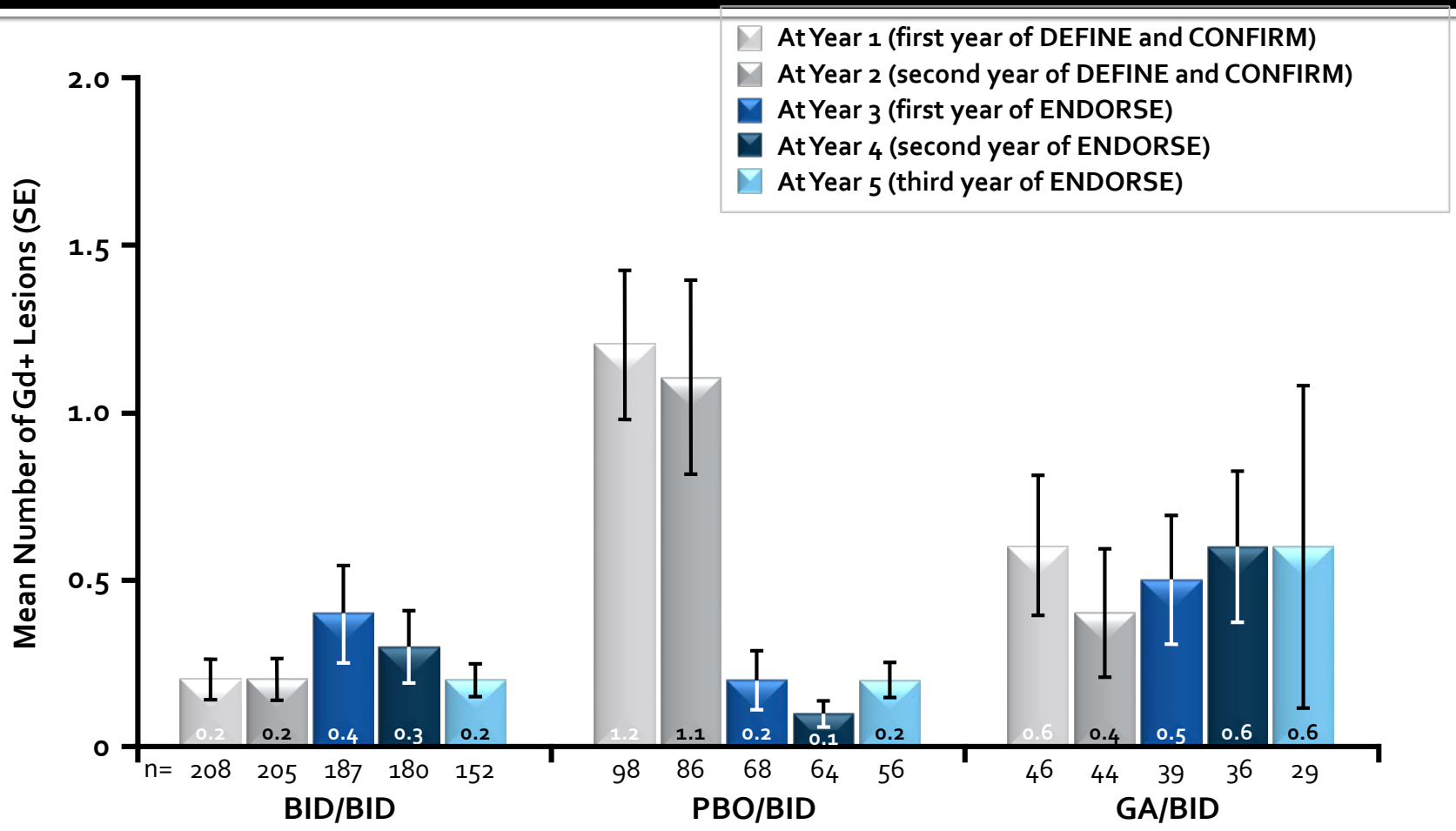
DEFINE, CONFIRM, ENDORSE için 5 Yıllık MRI Takip: Yeni/Genişleyen T2 lezyonlar



CI=confidence interval; PBO=placebo.

Arnold DL et al. Presented at ACTRIMS-ECTRIMS; 10–13 September 2014; Boston, MA, USA. P059.

DEFINE, CONFIRM, ENDORSE için 5 Yıllık MRI Takip: Gd+ Lezyonlar



SE=standard error; PBO=placebo.

Arnold DL et al. Presented at ACTRIMS-ECTRIMS; 10–13 September 2014; Boston, MA, USA. P059.

Neurol Ther (2016) 5:45–57
DOI 10.1007/s40120-016-0042-8

ORIGINAL RESEARCH

Sustained Effect of Delayed-Release Dimethyl Fumarate in Newly Diagnosed Patients with Relapsing–Remitting Multiple Sclerosis: 6-Year Interim Results From an Extension of the DEFINE and CONFIRM Studies

Ralf Gold · Gavin Giovannoni · J. Theodore Phillips · Robert J. Fox · Annie Zhang · Jing L. Marantz

Received: December 18, 2015 / Published online: March 1, 2016

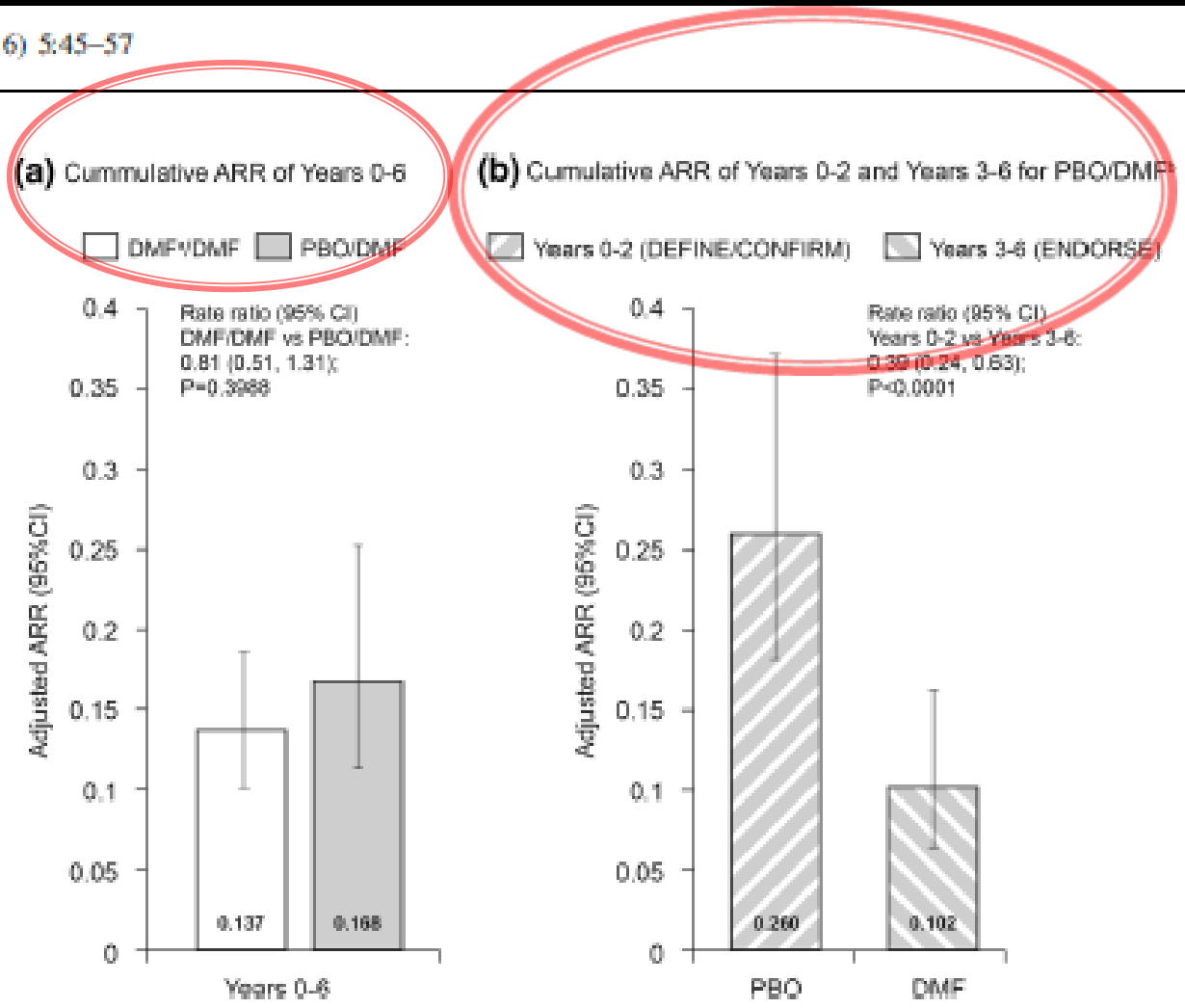


Fig. 1 Cumulative ARR. ARR was calculated using a negative binomial regression model, adjusted for baseline Expanded Disability Status Scale (≤2.0 vs. >2.0), baseline age (<40 vs. ≥40 years), region, and number of relapses in the 1 year prior to DEFINE/CONFIRM study entry. [a]*DMF* delayed-release dimethyl fumarate (also known as gastro-resistant DMF). [b]Based on a repeated negative binomial model for estimated 0–2/3–6 years ARR. *ARR* annualized relapse rate, *CI* confidence interval, *PBO* placebo

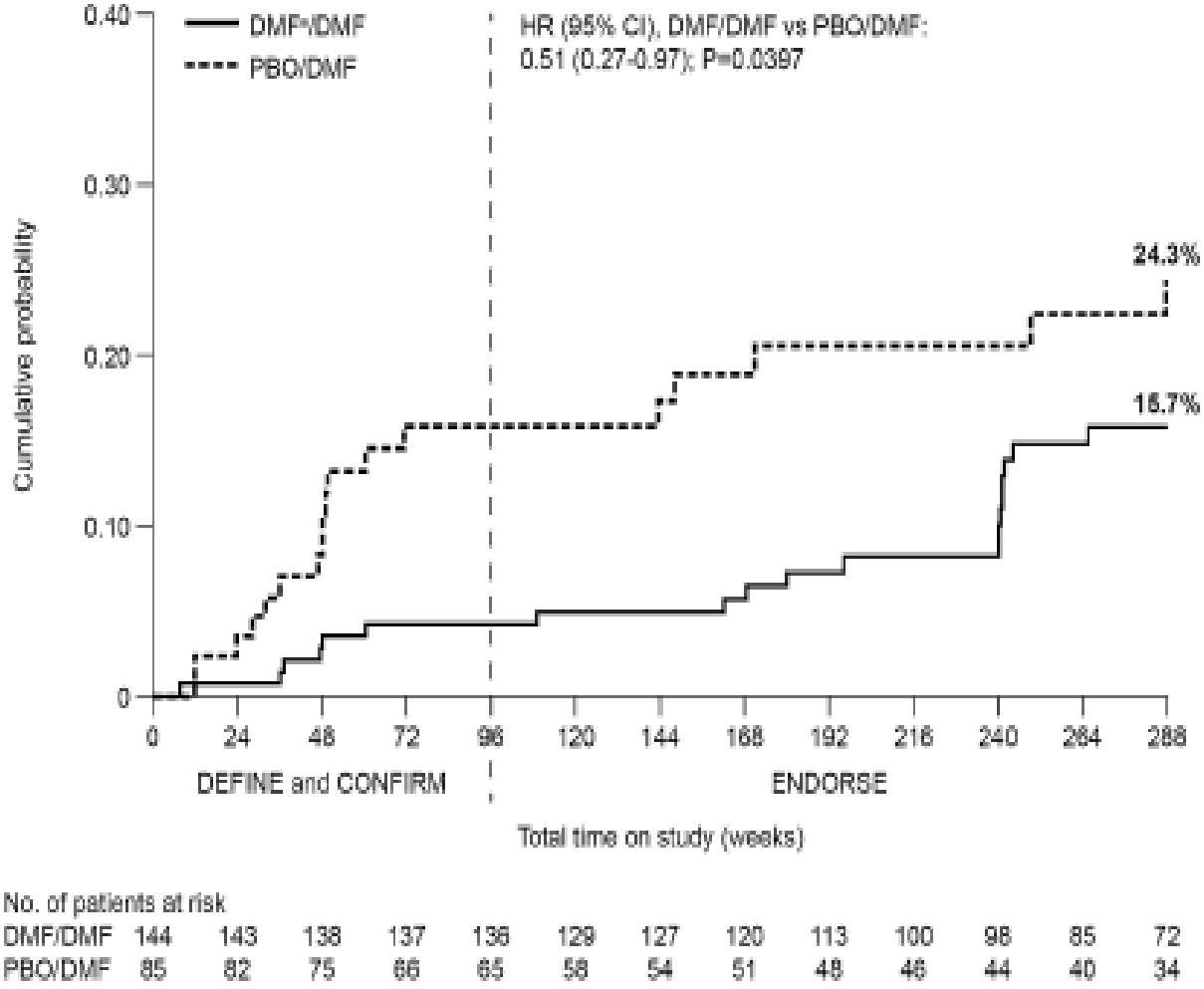
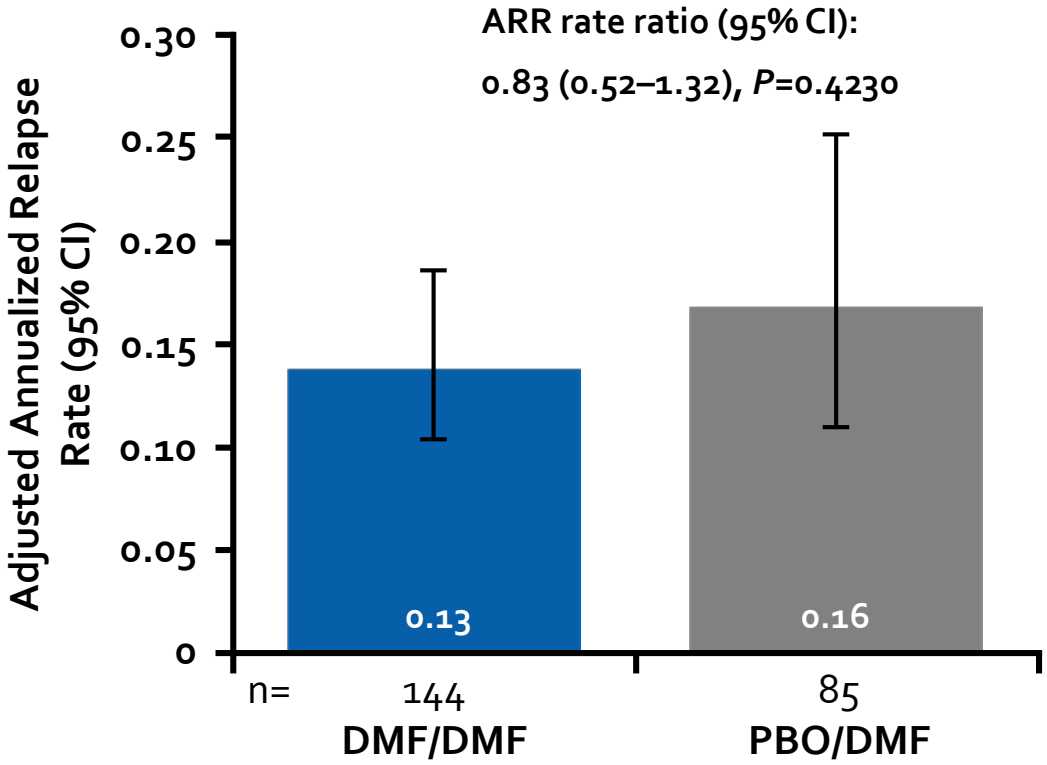


Fig. 2 Proportion of patients with 24-week confirmed disability progression. Confirmed progression of disability is defined as >1.0-point increase on EDSS from a baseline EDSS >1.0 confirmed for 24 weeks or >1.5-point increase on EDSS from a baseline EDSS of 0 confirmed for 24 weeks. Patients were censored if they withdrew from the study or switched to alternative MS medication without a progression. [a]*DMF* delayed-release dimethyl fumarate (also known as gastro-resistant DMF). *EDSS* Expanded Disability Status Scale, *HR* hazard ratio, *PBO* placebo

ENDORSE Yeni Teşhis Alan Hastalarda 7 Yıllık Ara Analiz : DEFINE / CONFIRM'ın Temelinden 7 Yıllık ARR



Based on negative binomial regression model adjusted for baseline EDSS (≤2.0 vs >2.0), baseline age (<40 vs ≥40 years), region, and number of relapses in the 1 year prior to DEFINE/CONFIRM study entry. ARR=annualized relapse rate; CI=confidence interval; DMF=dimethyl fumarate.
Gold R et al. Presented at ECTRIMS; September 14–17, 2016; London, UK. P631.

ENDORSE:8 yıllık Verileri

Efficacy of Delayed-release Dimethyl Fumarate in Newly Diagnosed Patients With Relapsing-Remitting Multiple Sclerosis: Eight-Year Follow-up of an Integrated Analysis of DEFINE, CONFIRM and ENDORSE

P661

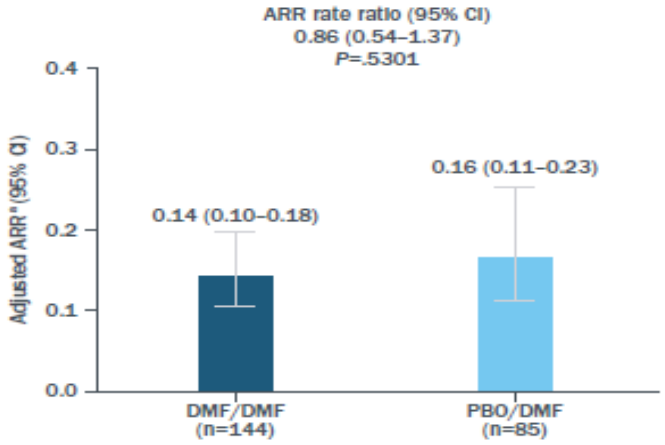
Gold R,[1] Giovannoni G,[2] Phillips JT,[3] Fox RJ,[4] Yang L,[5] Taylor C[5]

[1]Department of Neurology, St. Josef-Hospital, Ruhr University Bochum, Bochum, Germany; [2]Queen Mary University of London, Blizard Institute, London, UK; [3]Multiple Sclerosis Program, Baylor Institute for Immunology Research, Dallas, TX, USA; [4]Mellen Center for Multiple Sclerosis Treatment and Research, Cleveland Clinic, Cleveland, OH, USA; [5]Biogen, Cambridge, MA, USA

Conclusions

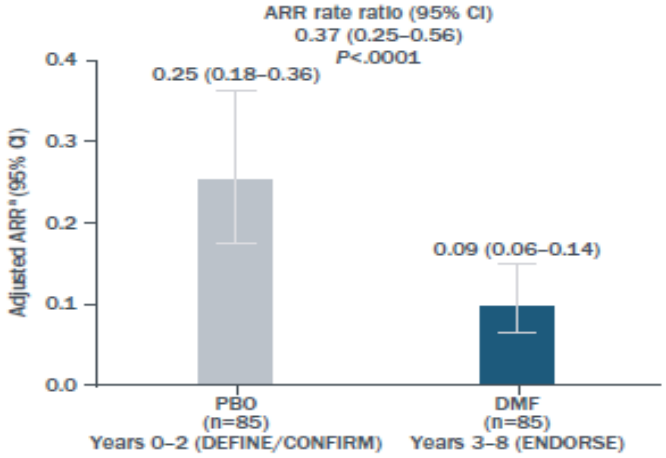
- Over ~8 years, ARR remained low in both newly diagnosed DMF/DMF and PBO/DMF patients.
- Adjusted ARR was significantly reduced in PBO/DMF patients after switching to DMF treatment.
- EDSS scores remained stable over 8 years, with >90% of patients maintaining walking abilities after 8 years of treatment, as measured by an EDSS score ≤3.5.

Figure 2. Adjusted ARR over 8 years (ENDORSE 6 years)



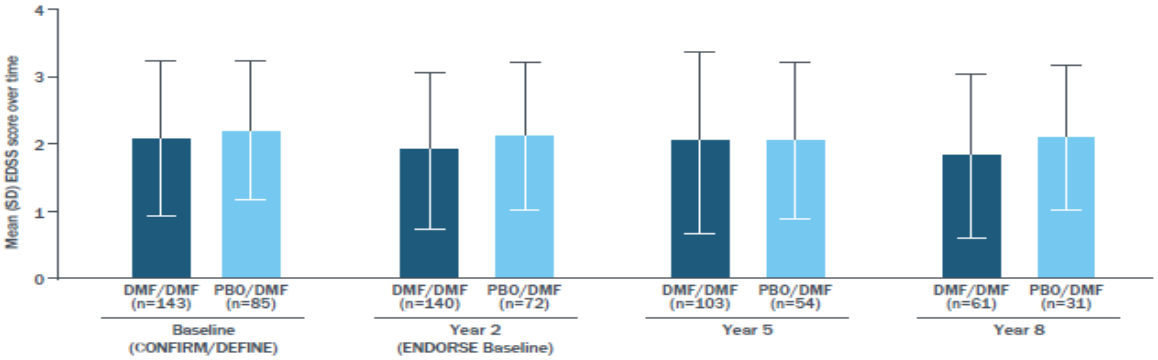
ARR = annualised relapse rate; DMF = delayed-release dimethyl fumarate; PBO = placebo
Continuous DMF treatment (DMF/DMF): Years 0–8 DMF
Delayed DMF treatment (PBO/DMF): Years 0–2 PBO; Years 3–8 DMF
[a]Based on negative binomial regression, adjusted for baseline Expanded Disability Status Scale score (≤2.0, >2.0), baseline age (<40, ≥40 years), region and number of relapses in the year before DEFINE/CONFIRM study entry

Figure 3. Adjusted ARR during Years 0–2 and Years 3–8 for PBO/DMF treatment group



ARR = annualised relapse rate; DMF = delayed-release dimethyl fumarate; PBO = placebo
[a]Based on a repeated negative binomial model for estimated ARR for Years 0–2 and Years 3–8

Figure 5. Mean EDSS score over time



DMF = delayed-release dimethyl fumarate; EDSS = Expanded Disability Status Scale; PBO = placebo

Table 1. Summary of newly diagnosed patients with EDSS score ≤3.5

Treatment group[a]	n (%)
DMF/DMF	
Year 2[b]	129 (93)
Year 8[c]	56 (92)
PBO/DMF	
Year 2[b]	65 (90)
Year 8[c]	29 (94)

DMF = delayed-release dimethyl fumarate; EDSS = Expanded Disability Status Scale; PBO = placebo
DEFINE/CONFIRM, 2 years; ENDORSE, 6 years for patients receiving continuous (DMF/DMF) and delayed (PBO/DMF) treatment
[a]There were <1% of PBO/DMF patients with EDSS score ≥6 at Year 2; no patients presented with EDSS score ≥6 at Year 8
[b]n=139 for DMF/DMF and n=72 for PBO/DMF
[c]n=61 for DMF/DMF and n=31 for PBO/DMF

Table 2. Clinical disease activity–free status over 8 years

Status	DMF/DMF n=144	PBO/DMF n=85
No relapses, %[a]	**58.3**	**55.3**
No 24-week CDP, %[b]	**84.0**	**77.6**
Clinical disease activity free, %[c]	**52.1**	**48.2**

CDP = confirmed disability progression; DMF = delayed-release dimethyl fumarate; PBO = placebo
[a]Relapse data after patients switched to alternative multiple sclerosis medications during the period were excluded
[b]CPD was defined as a ≥1.0-point increase on the Expanded Disability Status Scale (EDSS) from a baseline EDSS score ≥1 confirmed for 24 weeks, or a ≥1.5-point increase on the EDSS from a baseline EDSS score of 0 confirmed for 24 weeks. Patients were CDP censored if they withdrew from the study or switched to alternative multiple sclerosis medication without a progression
[c]Clinical disease activity free was defined as patients without relapse and without 24-week CDP

ECTRIMS,2017

Algoritma

- **RRMS hastalarında 1.basamak**

Fingolimod

Miracle drug for multiple sclerosis pirated from molecules in cordyceps mushrooms

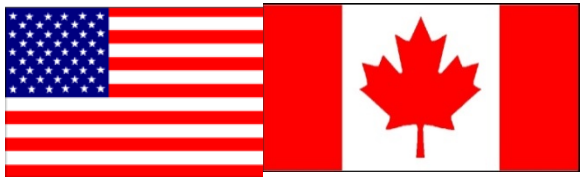
by Mike Adams, Natural News | published on March 7, 2013

A new "miracle" drug for the treatment of multiple sclerosis turns out to have been stolen ("derived") from cordyceps mushrooms. The drug is called Gilenya and it's being sold in the USA by Novartis AG — at the monopolistic price of $4,000 / month per person.

The drug is projected to be a blockbuster seller, with estimates putting it in the top 10 drugs by 2018 when it is expected to reach $5.3 billion in sales. A one-year course of Gilenya costs $48,000.

Fingolimod Onayları

Nisan, 2011



Eylül, 2010

Mart, 2011

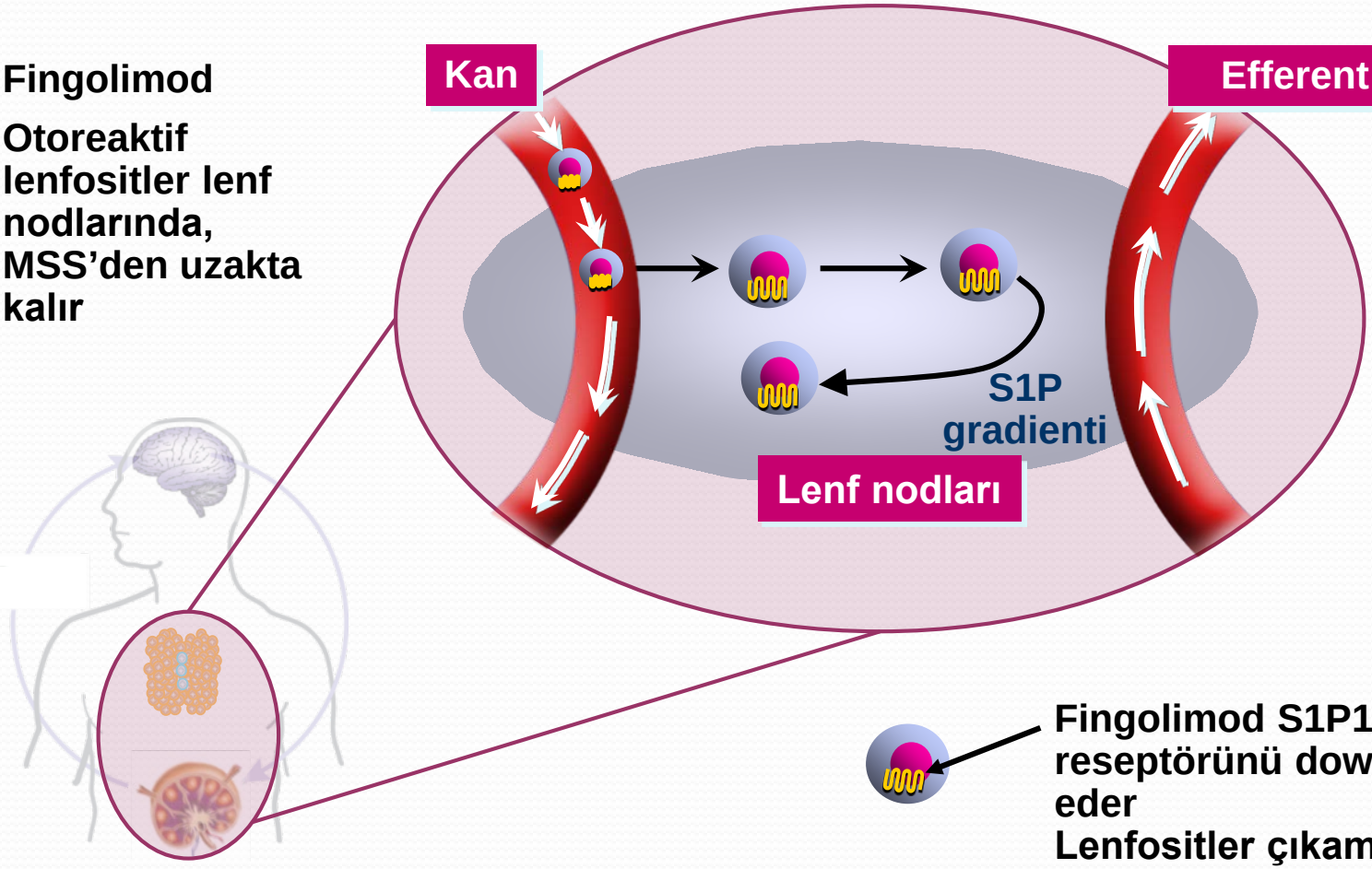
Fingolimod

- Gilenya  Fingya
- Vintor
- Findel
- Finimod
- Judexa
- Fingomes
- Fondos

Fingolimod lenf nodlarından lenfosit çıkışını engeller

Fingolimod

Otoreaktif lenfositler lenf nodlarında, MSS'den uzakta kalır

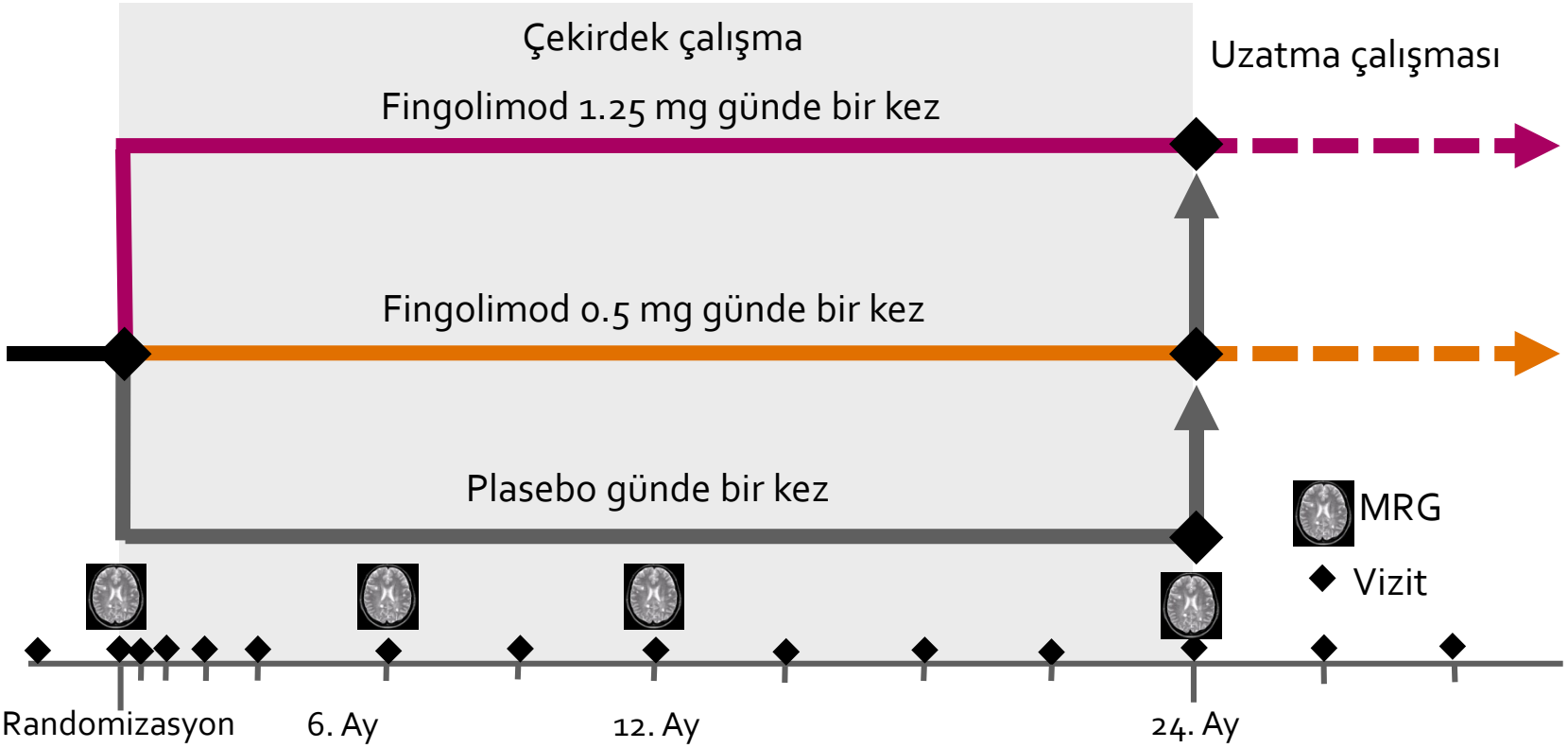


Fingolimod S1P1 reseptörünü down regüle eder
Lenfositler çıkamaz

Chun J, Hartung HP. Clin Neuropharmacol 2010; 33(2)91-101

FREEDOMS: Çalışma tasarımı

- **2 yıllık, randomize, çift kör, plasebo kontrollü, paralel gruplu, çok merkezli çalışma**
  - 138 merkezde randomize edilmiş,1272 hasta (22 ülke)
  - Merkezi MRG incelemesi ve bağımsız EDSS değerlendiriciler



EDSS, Genişletilmiş Özürlülük Durum Ölçeği; MRG, manyetik rezonans görüntüleme

TRANSFORMS: Çalışma tasarımı

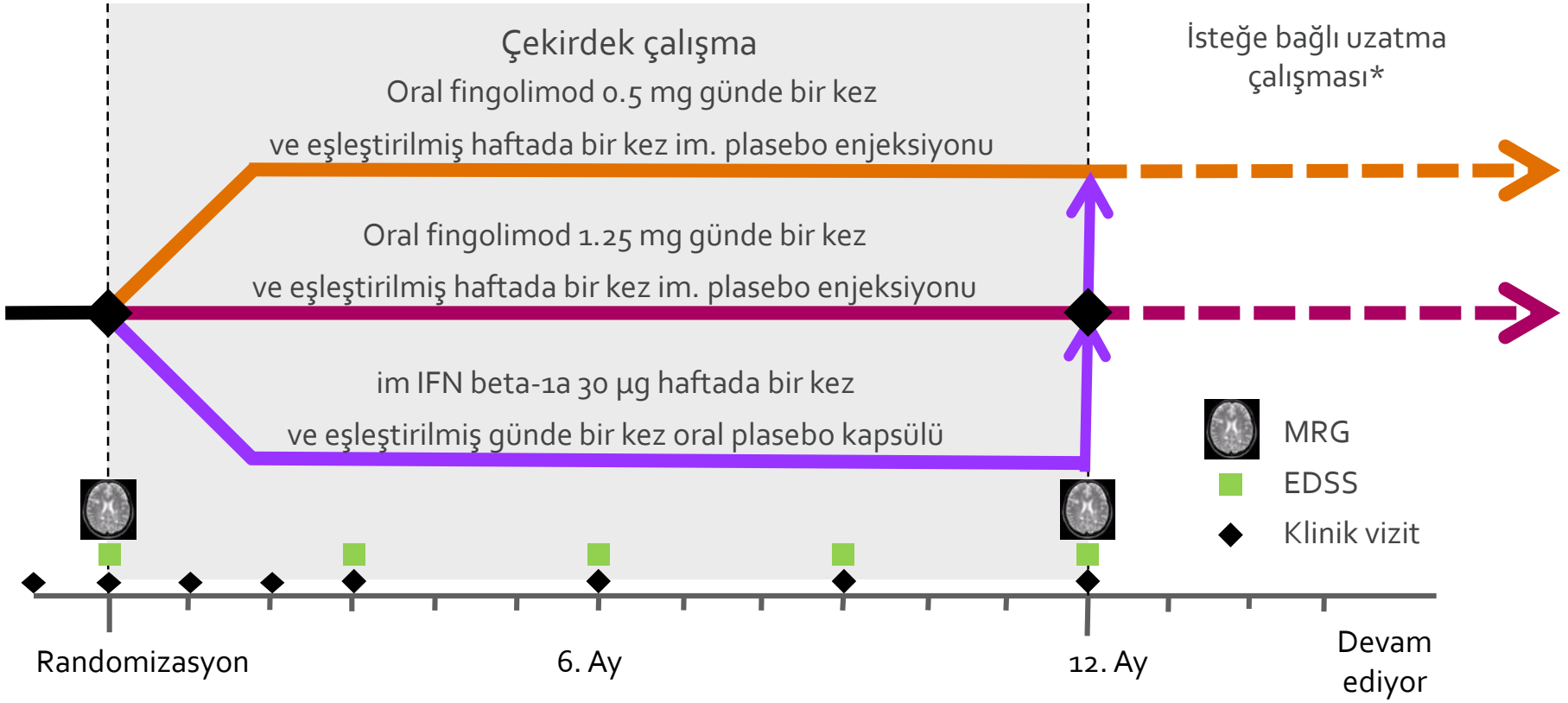
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis

Jeffrey A. Cohen, M.D., Frederik Barkhof, M.D., Giancarlo Comi, M.D., Hans-Peter Hartung, M.D., Bhupendra O. Khatri, M.D., Xavier Montalban, M.D., Jean Pelletier, M.D., Ruggero Capra, M.D., Paolo Gallo, M.D., Guillermo Izquierdo, M.D., Klaus Tiel-Wilck, M.D., Ana de Vera, M.D., James Jin, Ph.D., Tracy Stites, Ph.D., Stacy Wu, M.D., Shreeram Aradhye, M.D., and Ludwig Kappos, M.D., for the TRANSFORMS Study Group*

- **1 yıllık RRMS'de yapılan randomize, çift kör, çift plasebo, aktif kontrollü, çok merkezli çalışma**
  172 merkezde randomize edilmiş,1292 hasta (18 ülke)
  Merkezi MRG incelemesi ve bağımsız EDSS değerlendiriciler



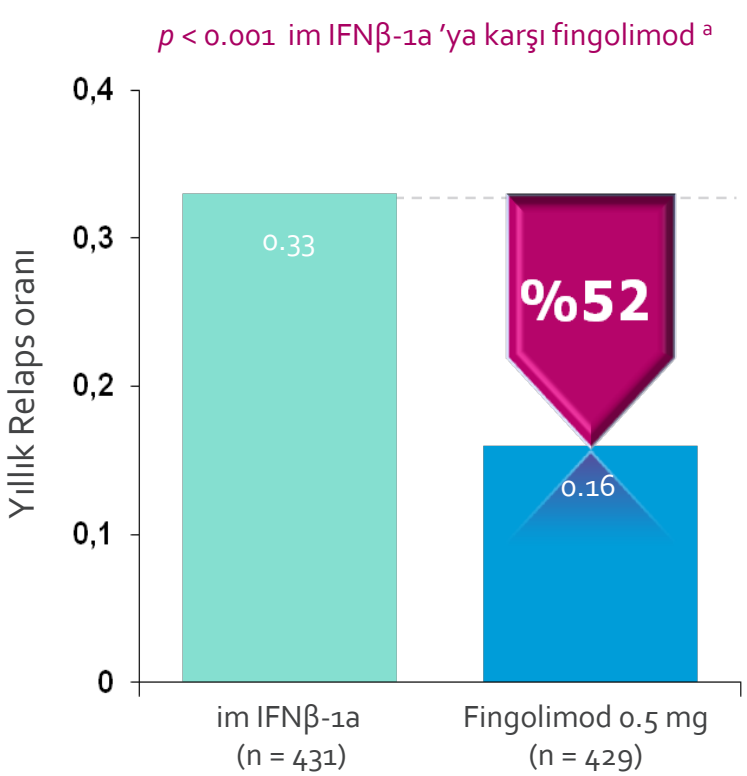
*Uzatma fazında im. IFN beta-1a grubundan katılımcılar fingolimod gruplarından birine randomize edilmiştir

EDSS, Genişletilmiş Özürlülük Durum Ölçeği; IFN, interferon; IM, intramüsküler; MRG, manyetik rezonans görüntüleme; RRMS, relapsing-remitting MS

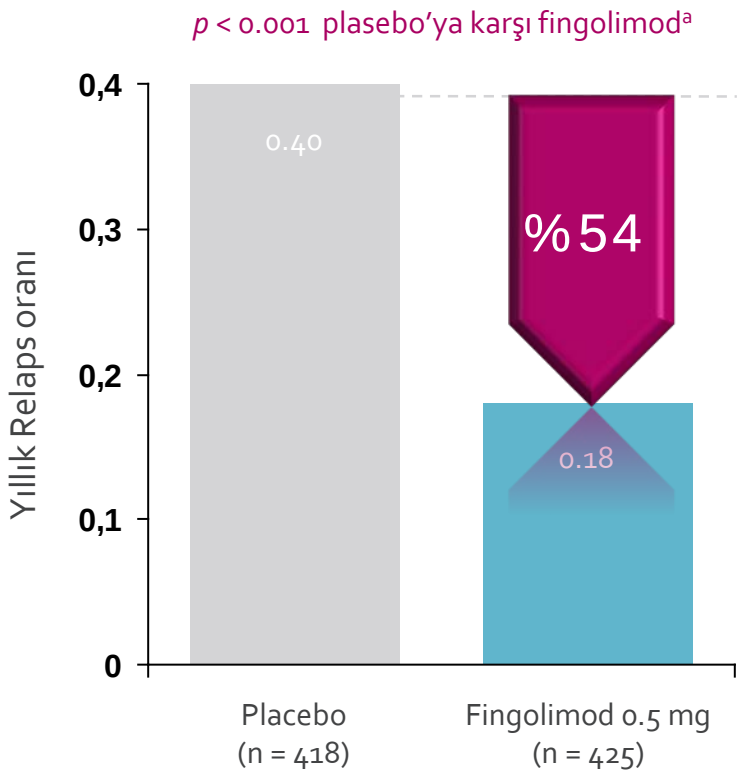
Cohen J. Oral presentation at *AAN* 2009

Fingolimod; Yıllık relaps oranında anlamlı azalma im IFNβ-1a ve plasebo karşısında

TRANSFORMS 1-yıl [1]



FREEDOMS 2-yıl [2]

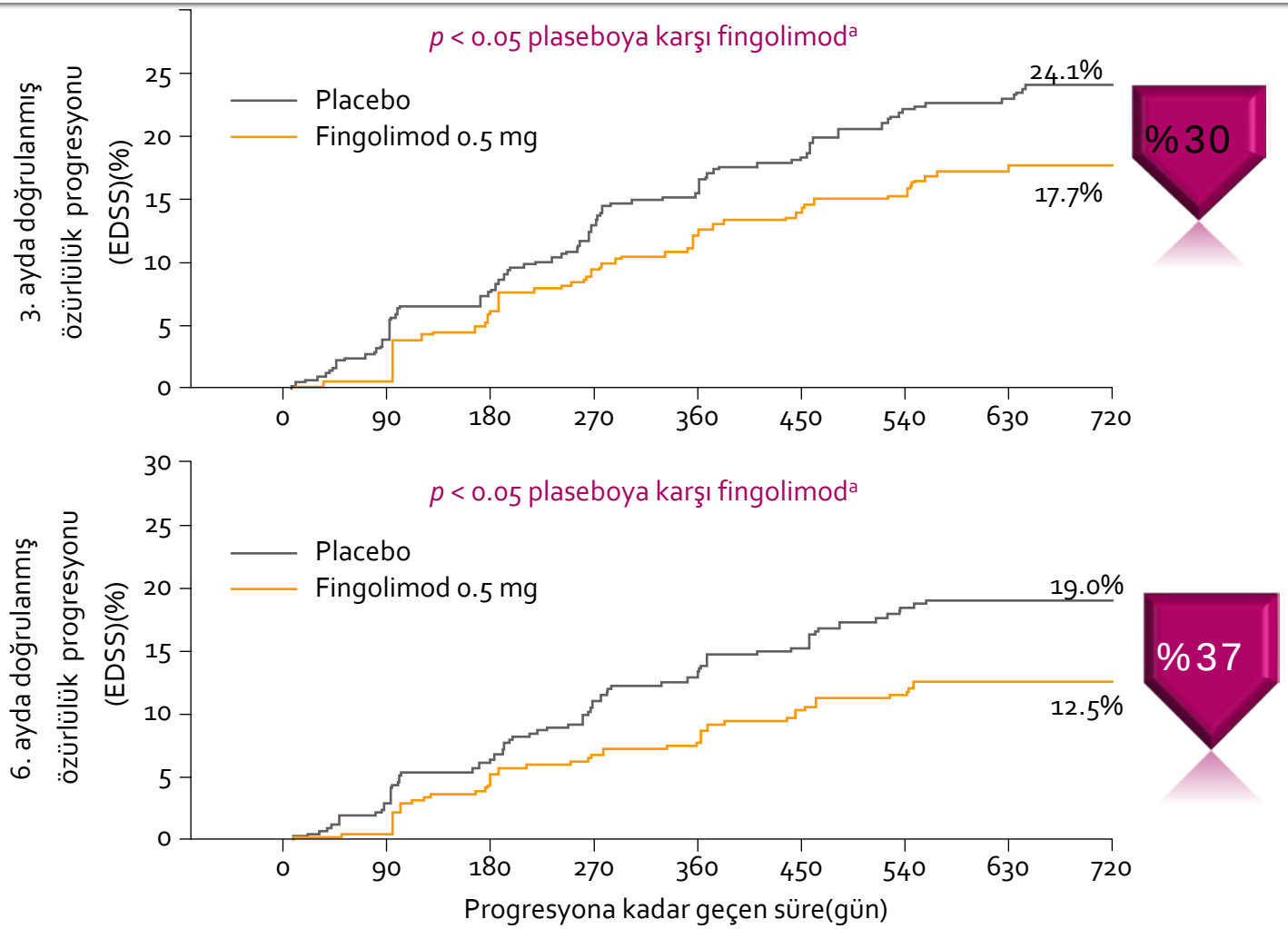


[a] Genişletilmiş Özürlülük Durum Ölçeği (EDSS) açısından düzeltilmiş negatif binominal regresyon modeli, im, intramüsküler.

1. Cohen JA *et al. N Engl J Med* 2010;362:402–15. 2. Kappos L *et al. N Engl J Med*. 2010;362:387–401.
FDA Advisory Committee presentation (10 June 2010).

EDSS ile ölçülen 3. ve 6. ayda doğrulanmış özürlülük progresyonu riskinde anlamlı azalma

FREEDOMS 2-yıl [2]



[a] Log-rank test comparing the survival distributions between treatment groups.

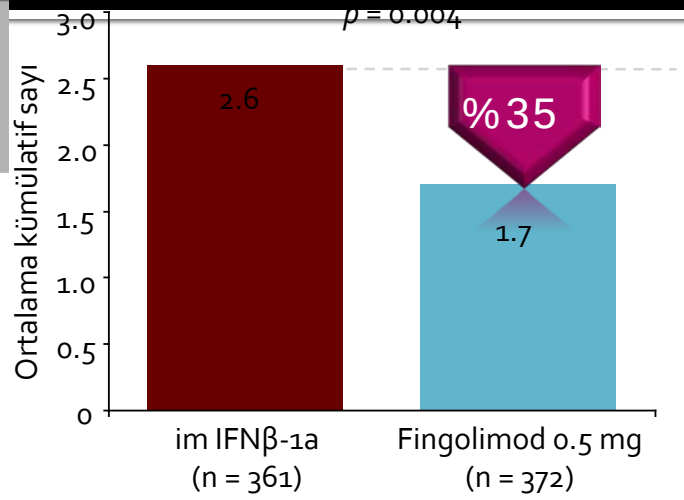
1. Kappos L *et al. N Engl J Med*. 2010;362:387–401. 2. Kappos L *et al. J Neurology*. 2010;257:S144 (abstract).

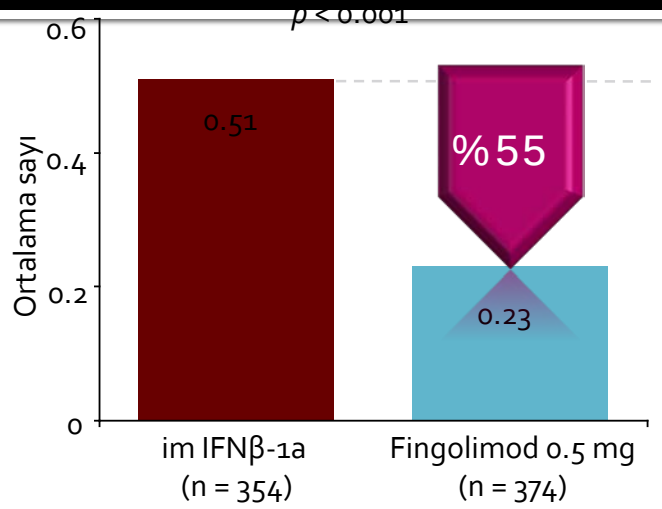
MRG lezyon aktivitesinde anlamlı azalma

Yeni oluşmuş/ büyümüş T2 lezyonlar

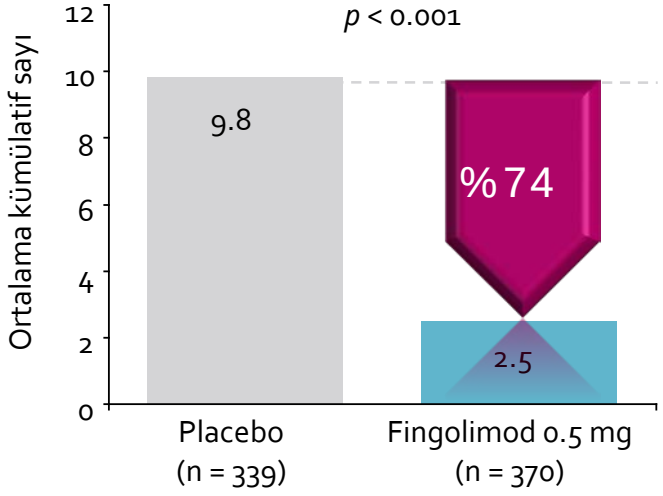
kontrastlı T1 lezyon

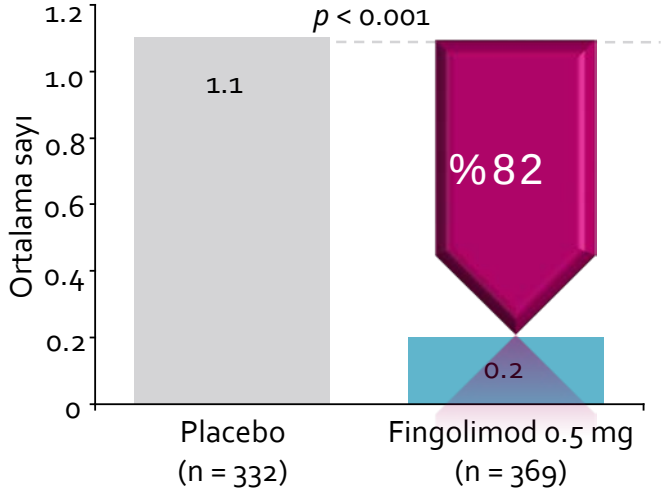
TRANSFORMS 1-yıl [1]





FREEDOMS 2-yıl 2



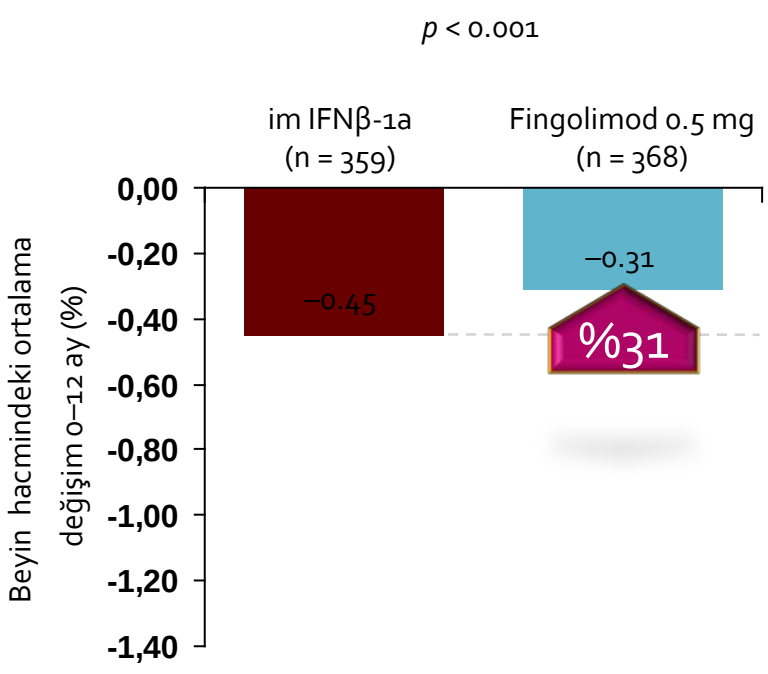


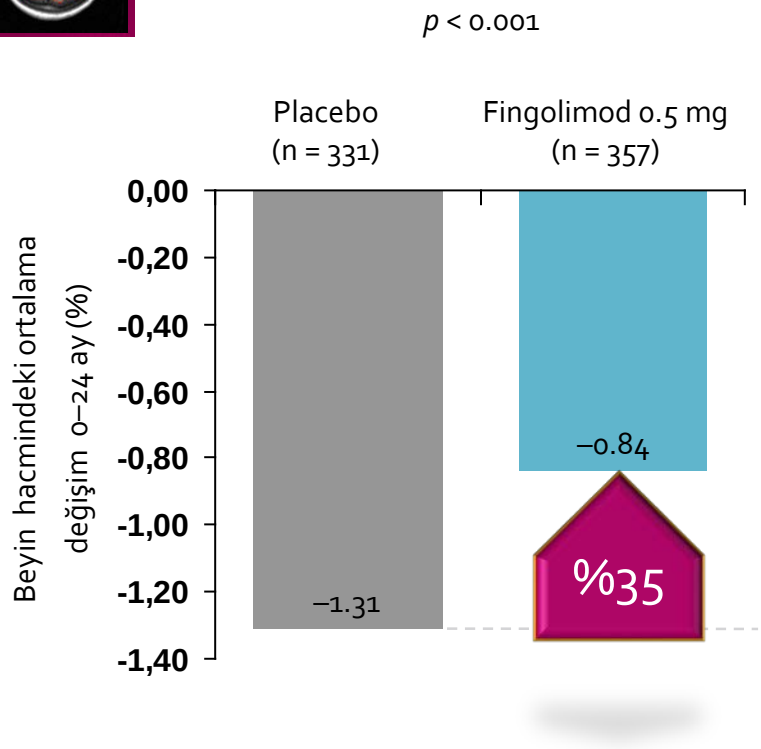
1. Cohen JA *et al. N Engl J Med* 2010;362:402–15. 2. Kappos L *et al. N Engl J Med* 2010;362:387–401.

Beyin atrofisi riskinde anlamlı azalma

TRANSFORMS 1-yıl [1]

FREEDOMS 2-yıl [2]

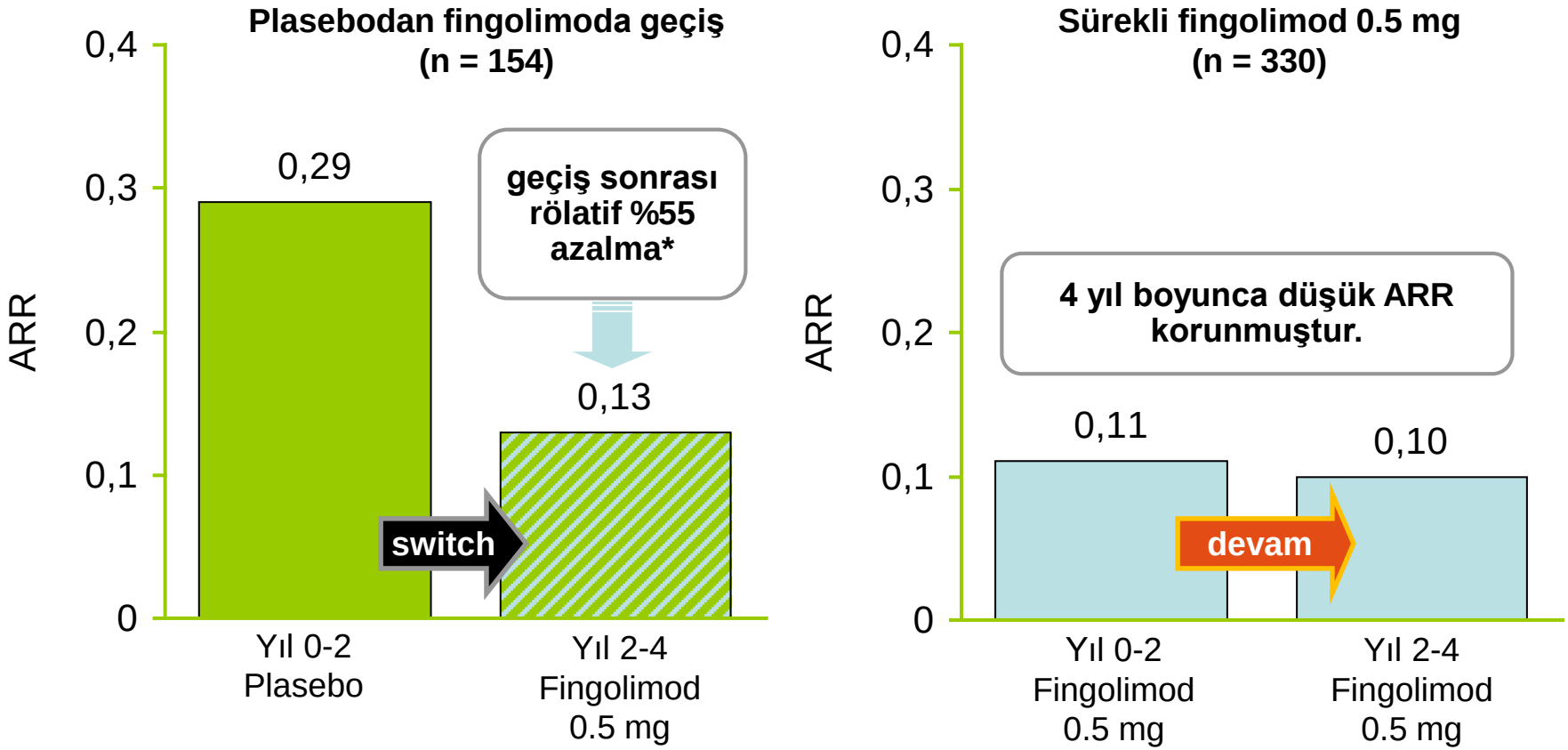




1. Cohen JA *et al. N Engl J Med* 2010;362:402–15. 2. Kappos L *et al. N Engl J Med* 2010;362:387–401.

Fingolimod uzun dönemde de relaps oranınında azalma sağlamıştır (FREEDOMS)

FREEDOMS uzatma: 4-yıllık sonuçlar[1,2]



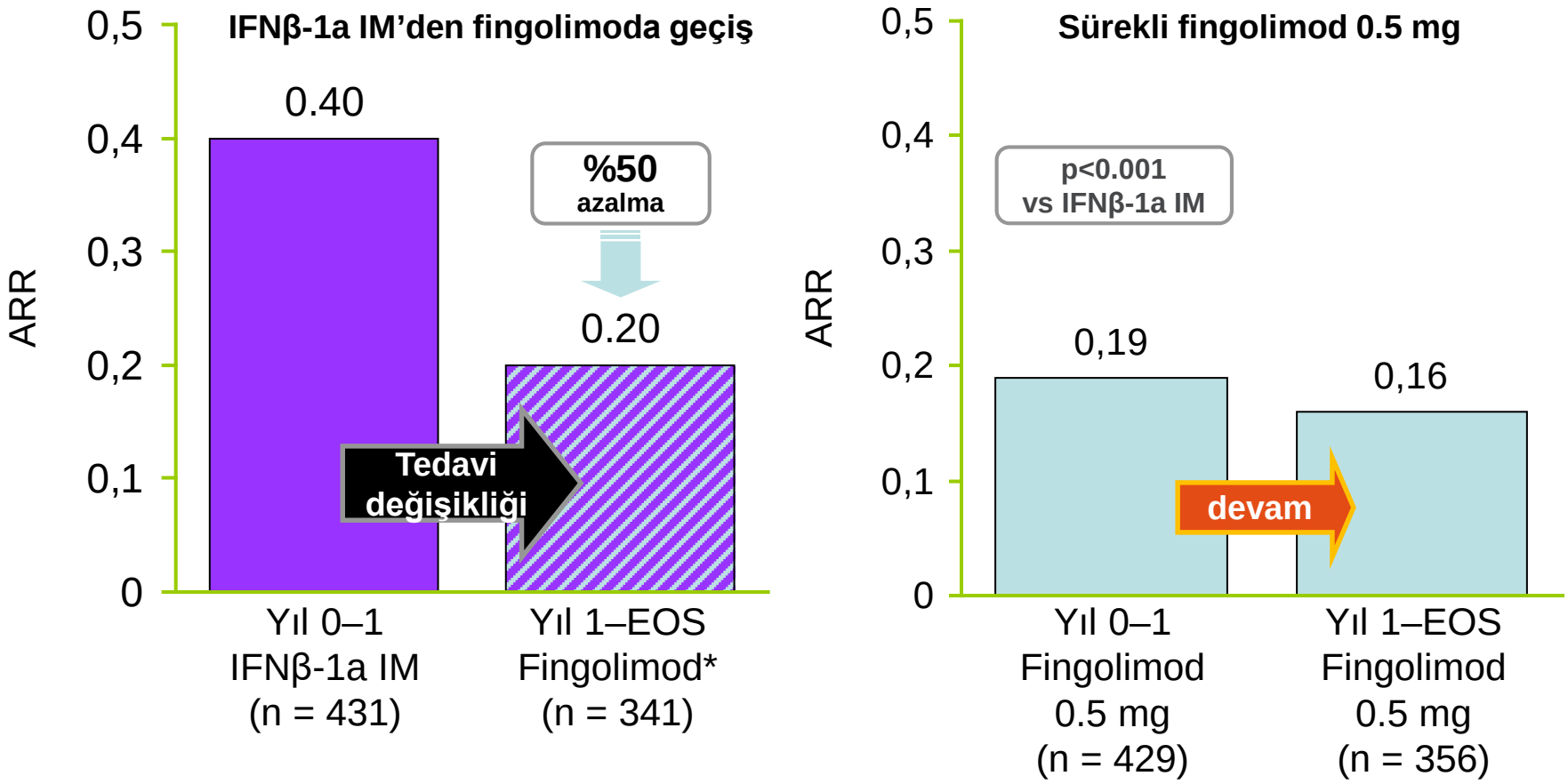
Extension ITT population. *p<0.001 vs Month 0–24

1. Kappos L *et al.* Oral presentation S41.004 at *AAN* 2012; 2. Kappos L *et al.* Poster P979 presented at *ECTRIMS* 2012

Fingolimod relaps oranında 4.5 yıl boyunca azalma sağlamıştır (TRANSFORMS)

TRANSFORMS uzatma

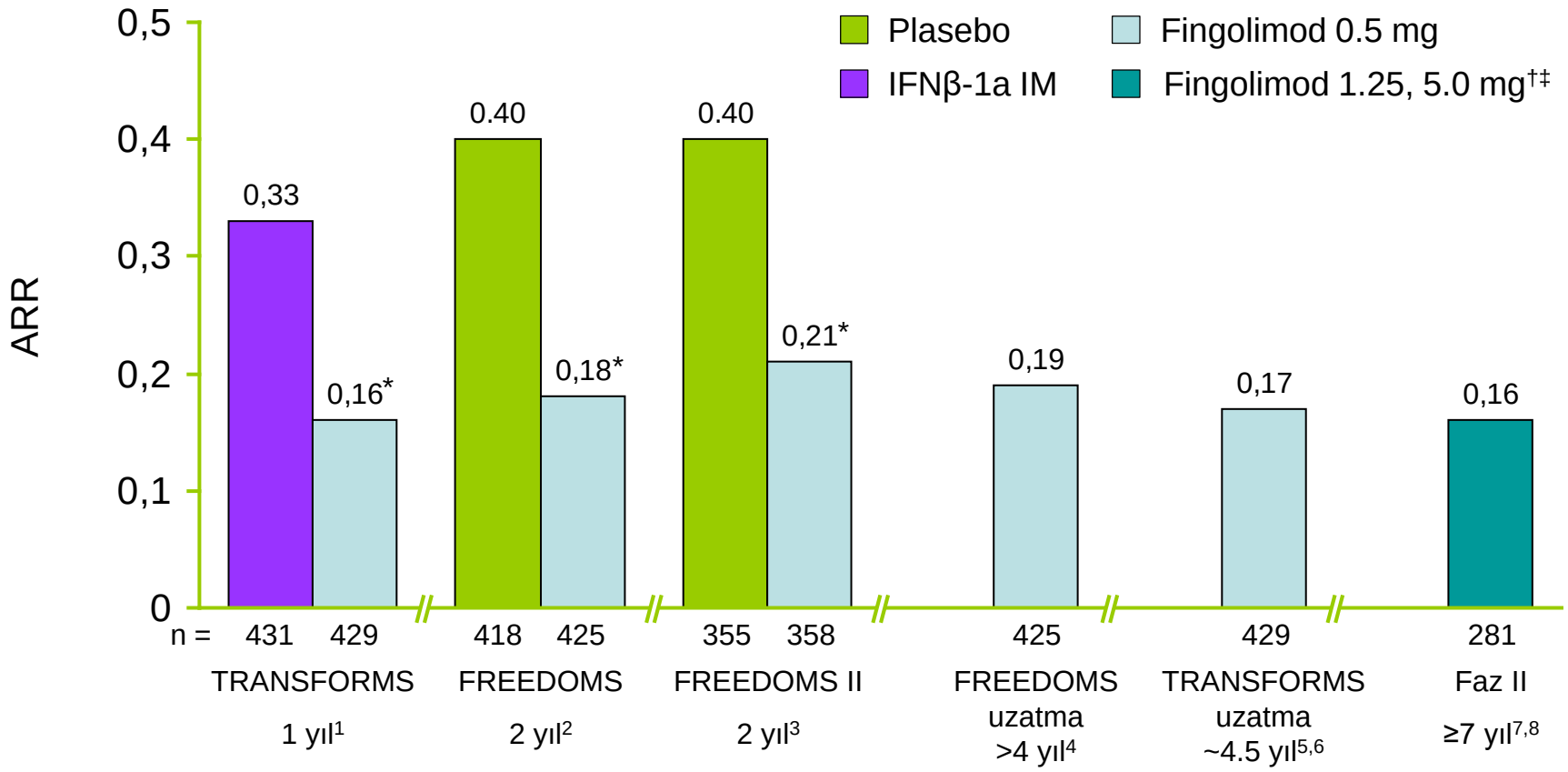
Ana çalışma (Yıl 0-1) vs uzatma fazı (Year 1-EOS-çalışmanın sonu)



Core ITT population. EOS (end of study) is the last available visit for the randomised patients between initiation and completion of the study. *In the extension, these patients were initially re-randomised to 0.5 or 1.25 mg fingolimod, and then all transitioned to open-label fingolimod 0.5 mg. Gilenya® 0.5 mg / day is the only dose approved for the treatment of MS. Khatri B *et al*. Oral 218 presented at *ENS* 2012

Fingolimod ile ARR'deki azalmanın uzun dönem çalışmalarda devam ettiği görülmüştür

Fingolimod Faz II and III çalışmalar

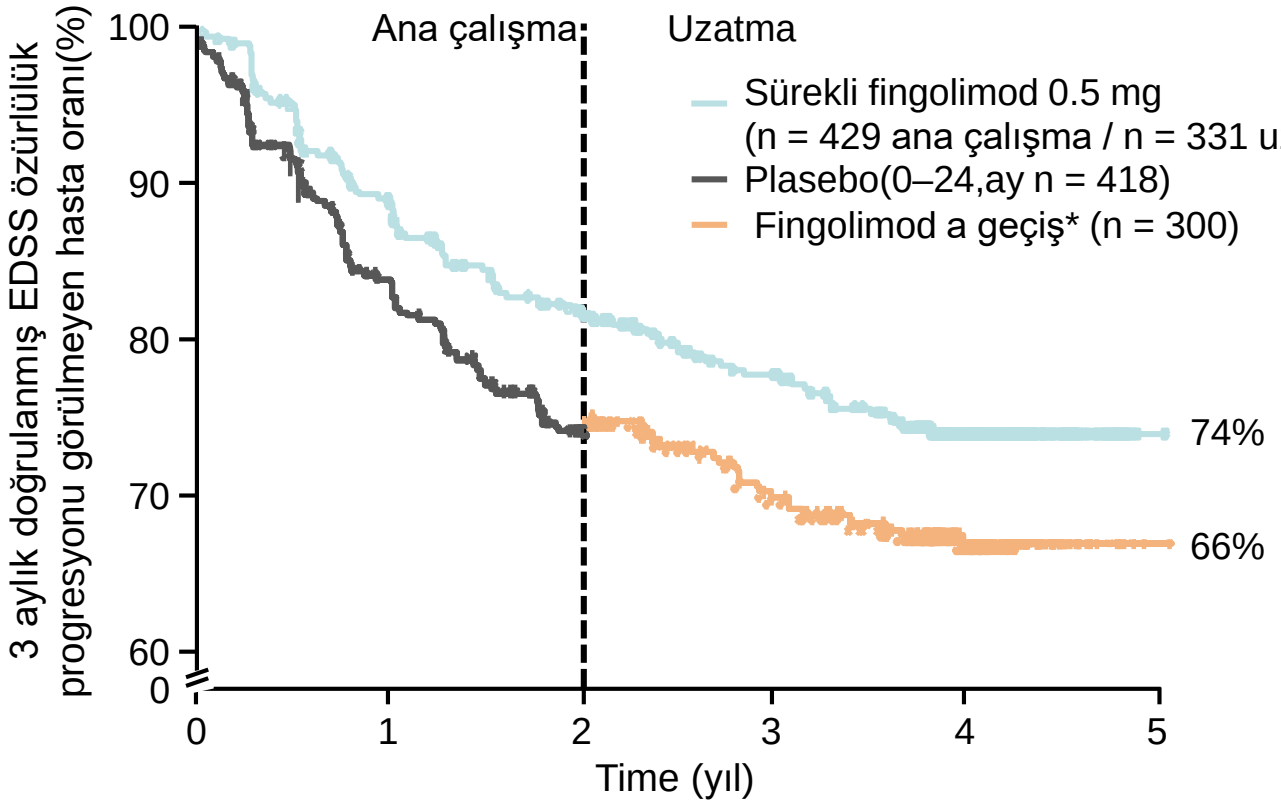


*p<0.001 vs respective control; †patients may have received placebo for 6 months in the core study before switching to fingolimod 1.25 mg or 5.0 mg. Patients on fingolimod 5.0 mg were switched to open-label fingolimod 1.25 mg in Months 15-24. All patients transitioned to fingolimod 0.5 mg after 5 years until study end; ‡Gilenya® 0.5 mg / day is the only dose approved for the treatment of MS

1. Cohen JA *et al. N Engl J Med* 2010; 2. Kappos L *et al. N Engl J Med* 2010; 3. Calabresi PA *et al.* Poster P491 presented at *ECTRIMS* 2012; 4. Kappos L *et al.* Oral presentation S41.004 at *AAN* 2012; 5. Khatri B *et al.* Poster 218 presented at *ENS* 2012; 6. Montalban X *et al.* Poster P517 presented at *ECTRIMS* 2012; 7. Antel J *et al.* Oral presentation P01.129; at *AAN* 2012; 8. Montalban X *et al.* Poster P348 presented at *ENS* 2012

Fingolimod 4 yıl boyunca özürlülük gelişim riskini azaltmıştır

FREEDOMS uzatma: >4-yıllık sonuçlar



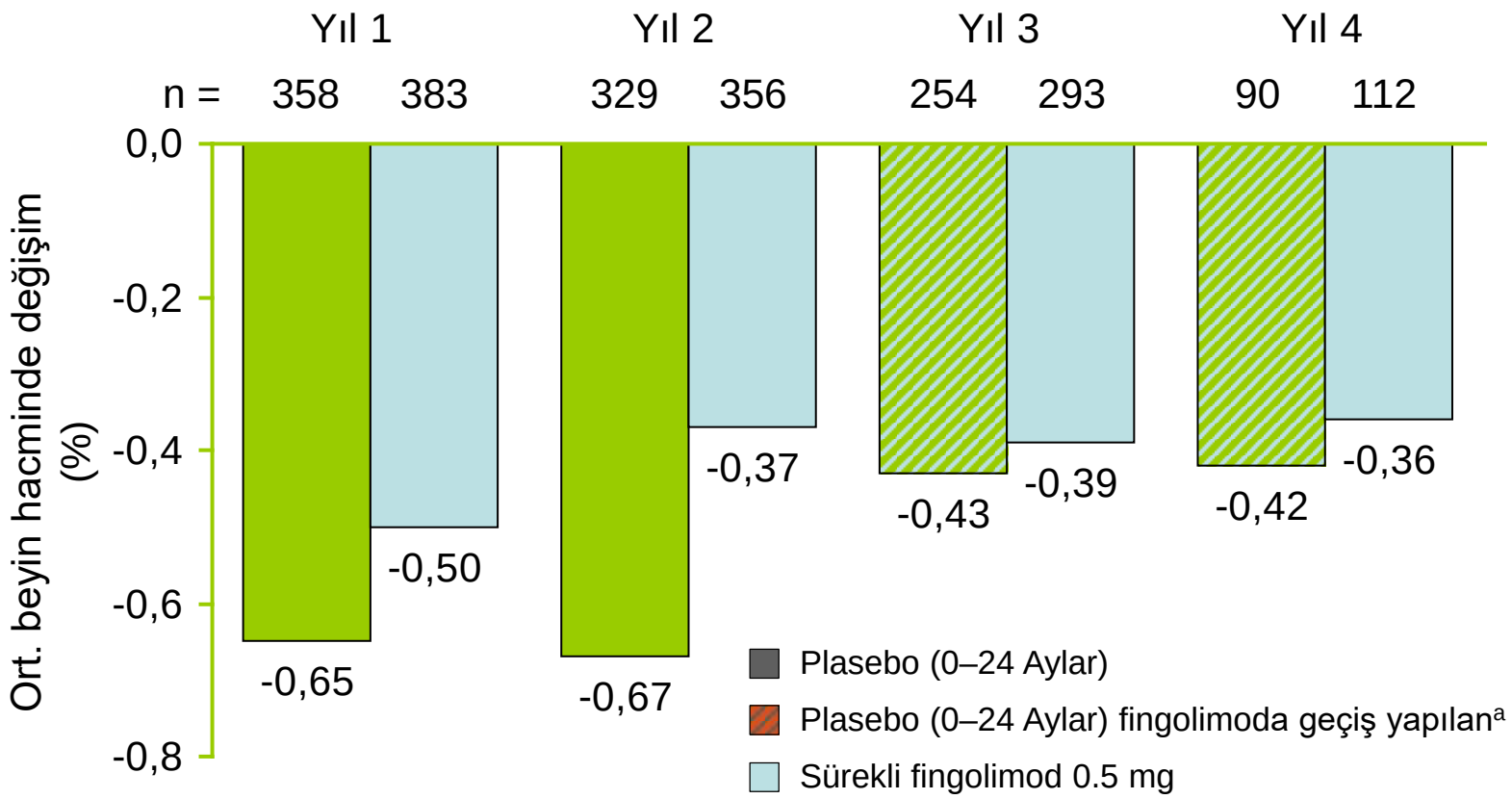
HR: 0.73; p=0.017

%27 progresyon riskinde rölatif azalma

4. yılda özürlülük görülmeyen hasta oranı fingolimod ile plaseboya kıyasla daha yüksektir. Bu da erken tedavinin yararını desteklemektedir.

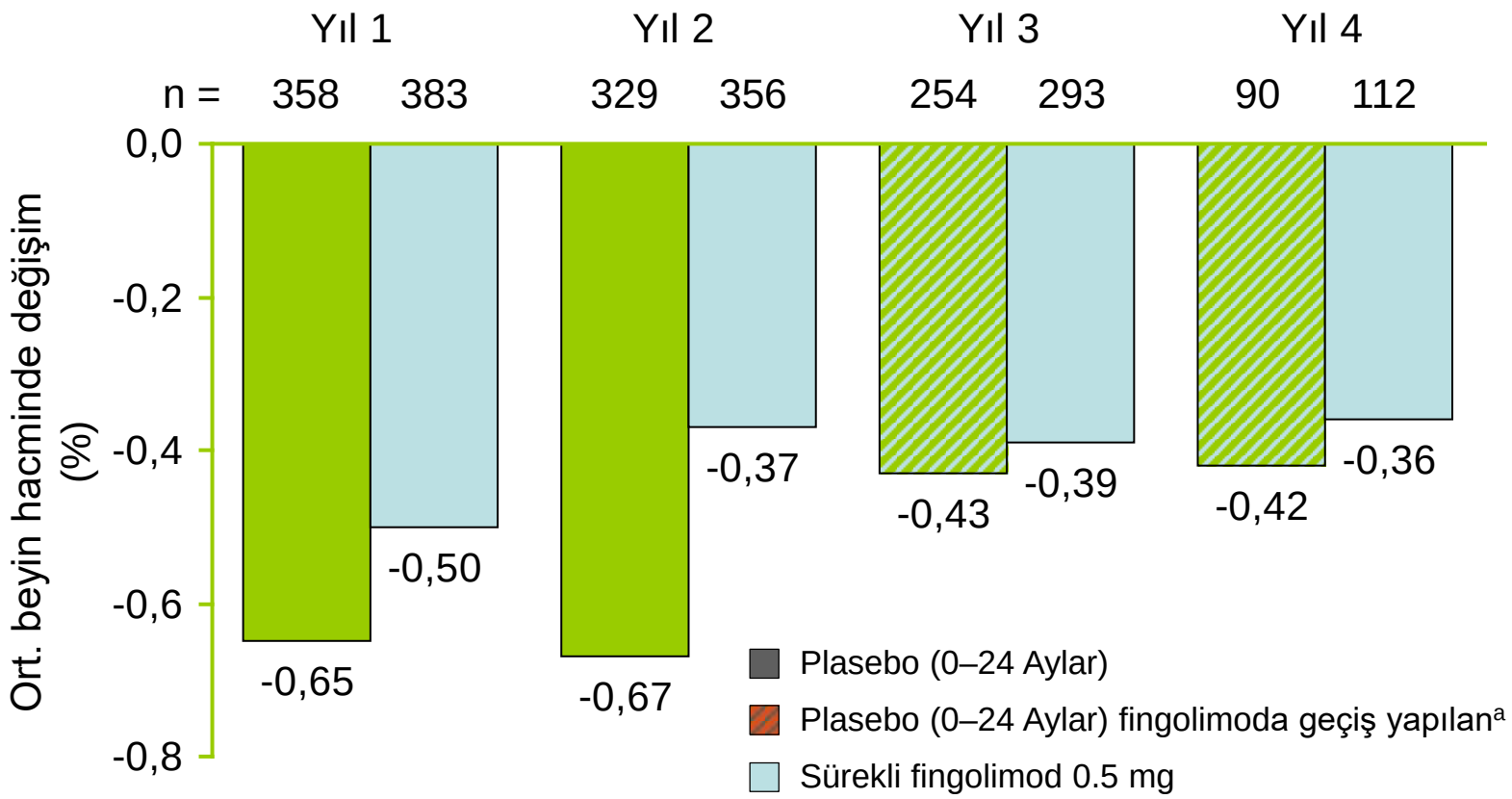
Time to first 3-month confirmed disability progression. Core ITT population (Kaplan–Meier estimate); *In the extension, these patients were initially re-randomized to 0.5 or 1.25 mg fingolimod, and then all transitioned to open-label fingolimod 0.5 mg. Gilenya® 0.5 mg / day is the only dose approved for the treatment of MS. Kappos L *et al.* Oral presentation S41.004 at *AAN* 2012

FREEDOMS uzatma çalışması: fingolimod tedavisi 4 yılda beyin hacim kaybında kalıcı azalma sağlamıştır



Core ITT population. [a]In the extension, these patients were initially re-randomised to fingolimod 0.5 or 1.25 mg, and then all transitioned to open-label fingolimod 0.5 mg. Gilenya® 0.5 mg / day is the only dose approved for the treatment of MS. No statistical analysis was performed
n, number of patients with non-missing values. Radue EW *et al*. Oral O219 presented at *ENS* 2012

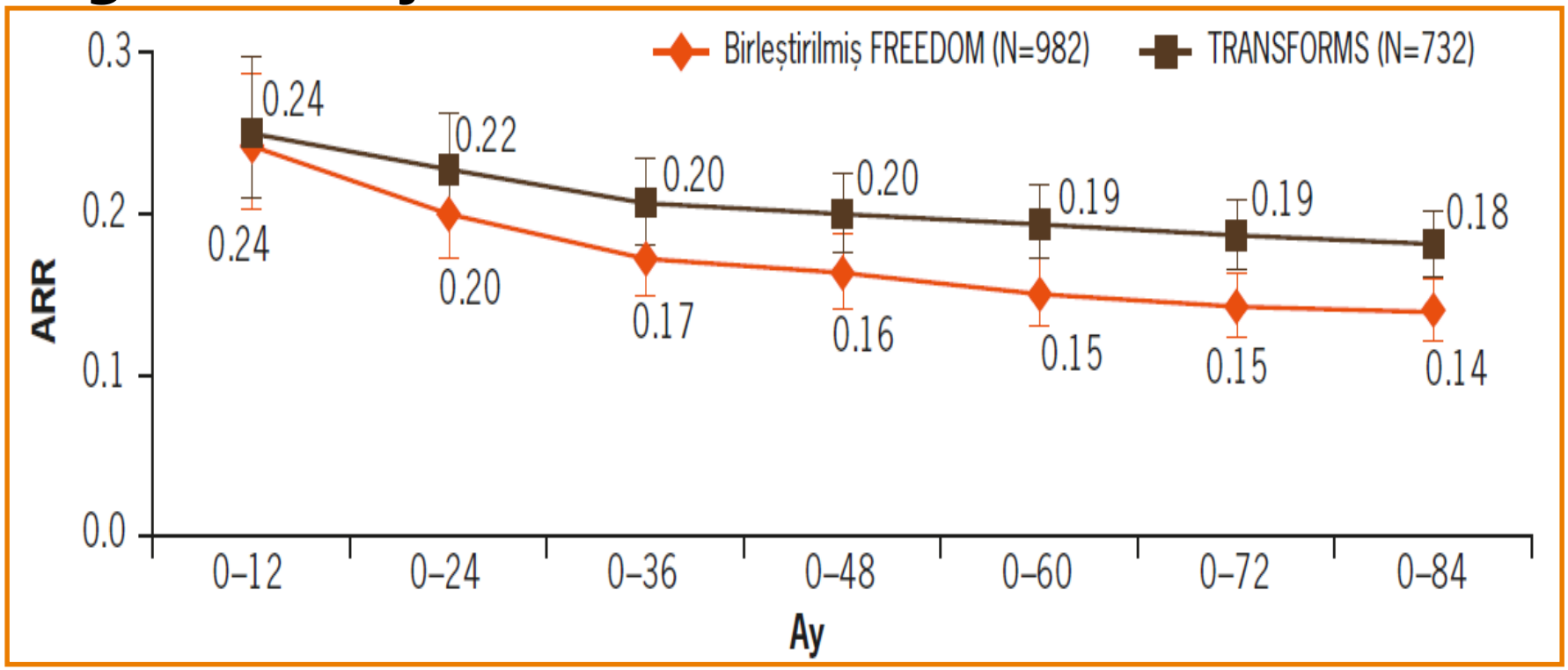
FREEDOMS uzatma çalışması: fingolimod tedavisi 4 yılda beyin hacim kaybında kalıcı azalma sağlamıştır



Core ITT population. [a]In the extension, these patients were initially re-randomised to fingolimod 0.5 or 1.25 mg, and then all transitioned to open-label fingolimod 0.5 mg. Gilenya® 0.5 mg / day is the only dose approved for the treatment of MS. No statistical analysis was performed
n, number of patients with non-missing values. Radue EW *et al*. Oral O219 presented at *ENS* 2012

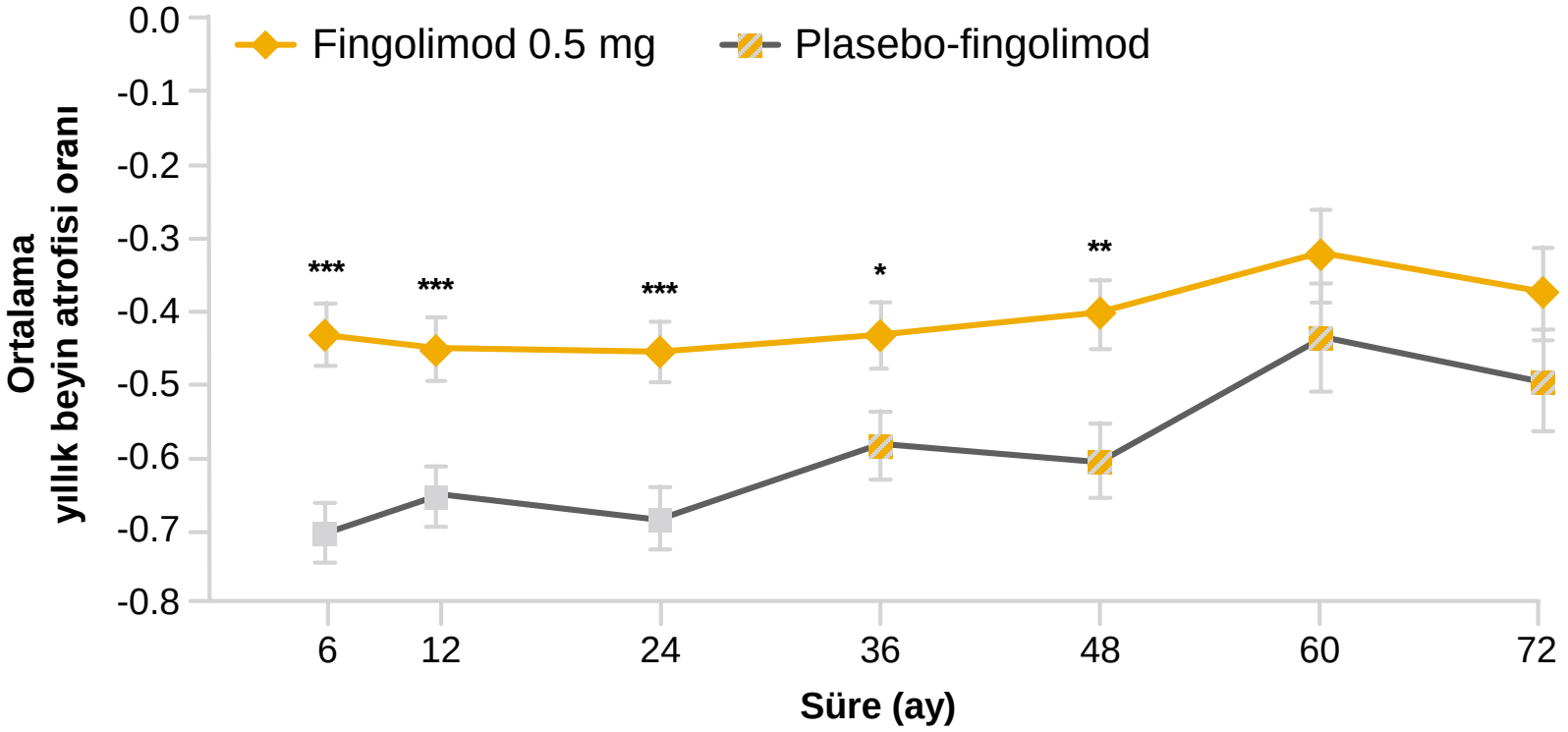
Fingolimodun Relapslar üzerine etkisi

7 yıl boyunca devam eden yüksek etkinlik gösterilmiştir.



Cohen J., Pradhan A, Gottschalk R, Chen Yu, Kappos L. **Ongoing safety and effectiveness: An interim analysis of long-term fingolimod treatment,** P3.057 Poster presented at the 68th Congress of the American Academy of Neurology, April 15–21, 2016

Fingolimodun Atrofi üzerine etkisi

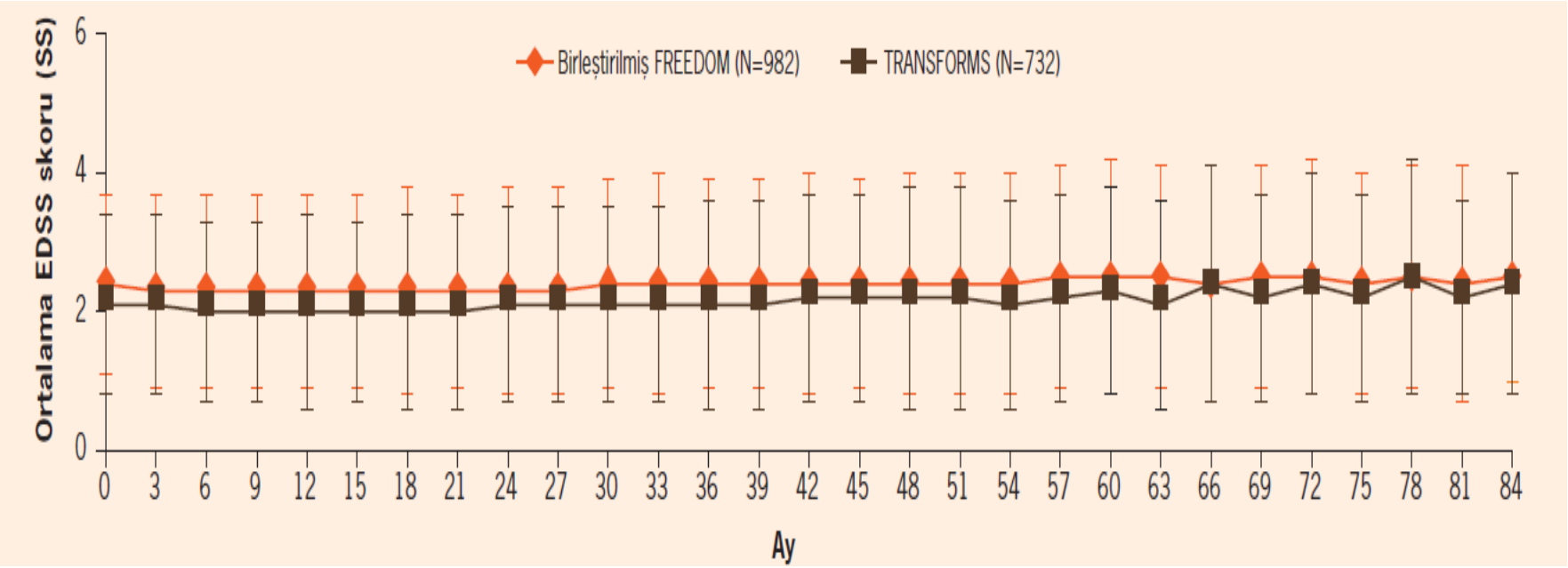


Fingolimod 0.5 mg, n	714	687	642	455	368	175	243
Plasebo-fingolimod, n	709	655	599	409	314	128	202

RRMS'te fingolimodun araştırıldığı Faz II, III ve IIIb çalışmalarının LONGTERMS uzatma fazı. *p<0.05; **p<0.01; *plasebo-fingolimod grubuna kıyasla p<0.001 LS, en küçük kareler; SEM, standart ortalama hata Radue EW *ve ark.*. Poster P439 presented at *ECTRIMS-ACTRIMS* 2014, with kind permission

1.Tedavi Geçişinde Etkinlik

Klinik Çalışma : 7 yıl boyunca stabil devam eden ortalama EDSS skoru

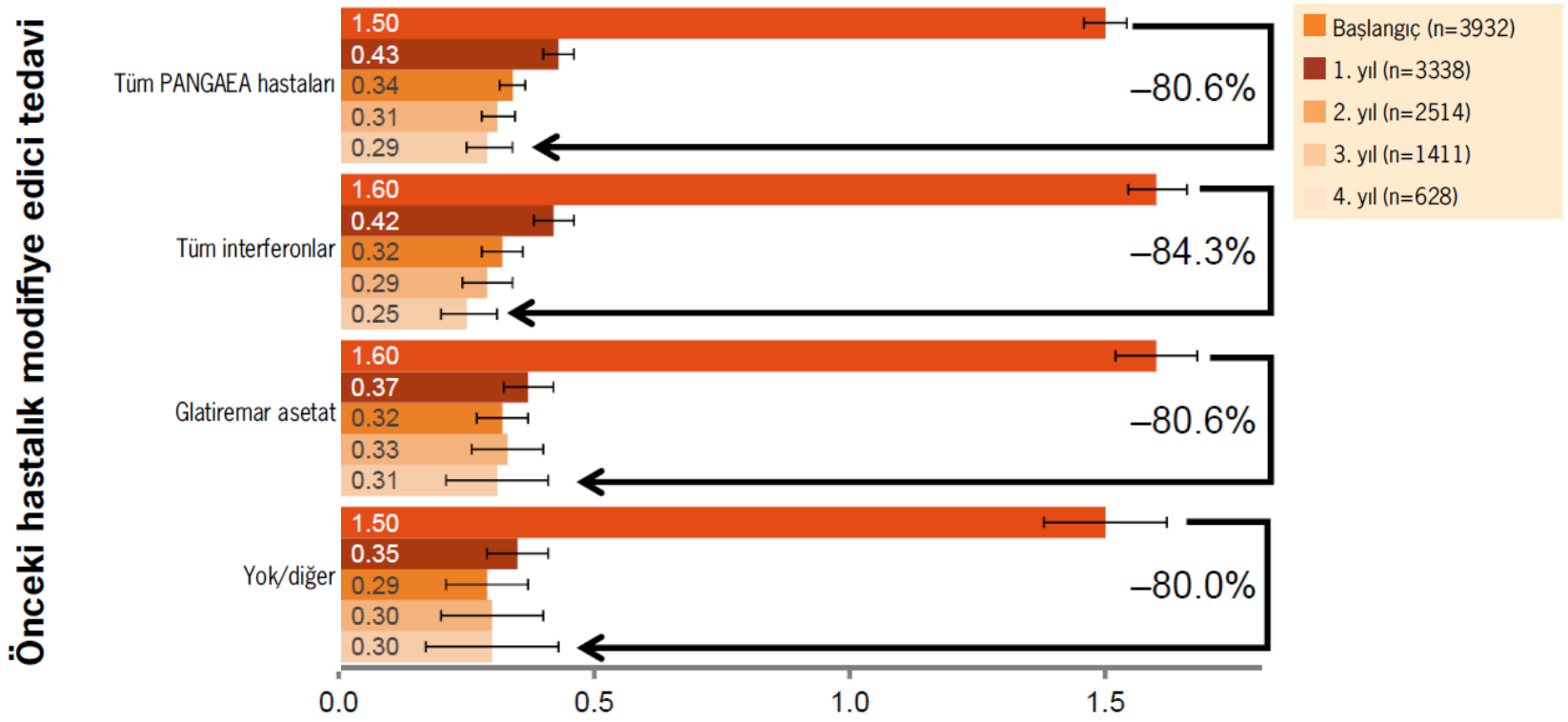


Cohen J., Pradhan A, Gottschalk R, Chen Yu, Kappos L. **Ongoing safety and effectiveness: An interim analysis of long-term fingolimod treatment,** P3.057 Poster presented at the 68th Congress of the American Academy of Neurology, April 15–21, 2016

1.Tedavi Geçişinde Etkinlik

Gerçek Yaşam Çalışması: Fingolimod'a tedavi değişimi

PANGAEA : ~ 4000 MS hastası

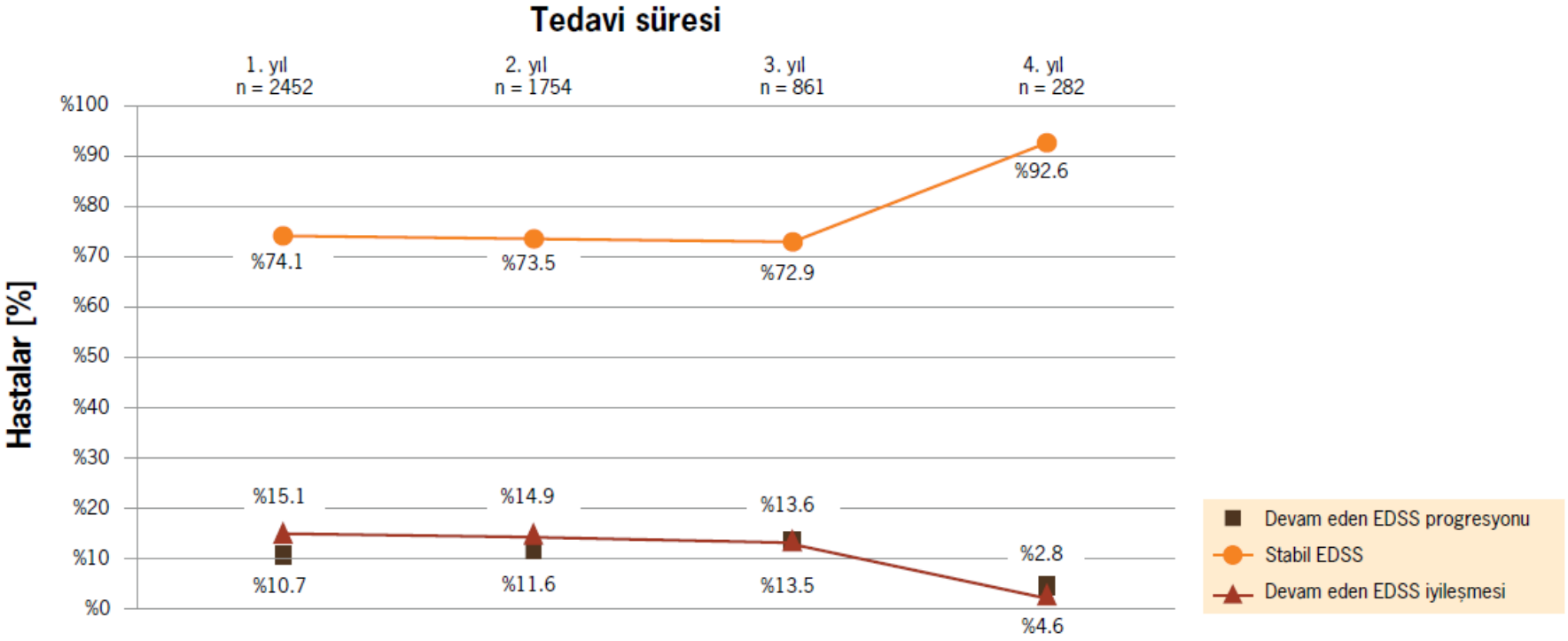


Ziemssen T, *et al.* AAN 2016; Abstract P3.072 (Poster).

1.Tedavi Geçişinde Etkinlik

Gerçek Yaşam Çalışması: Fingolimod'a tedavi değişimi

PANGAEA : 4. yılda özürlülük değerlendirmesi

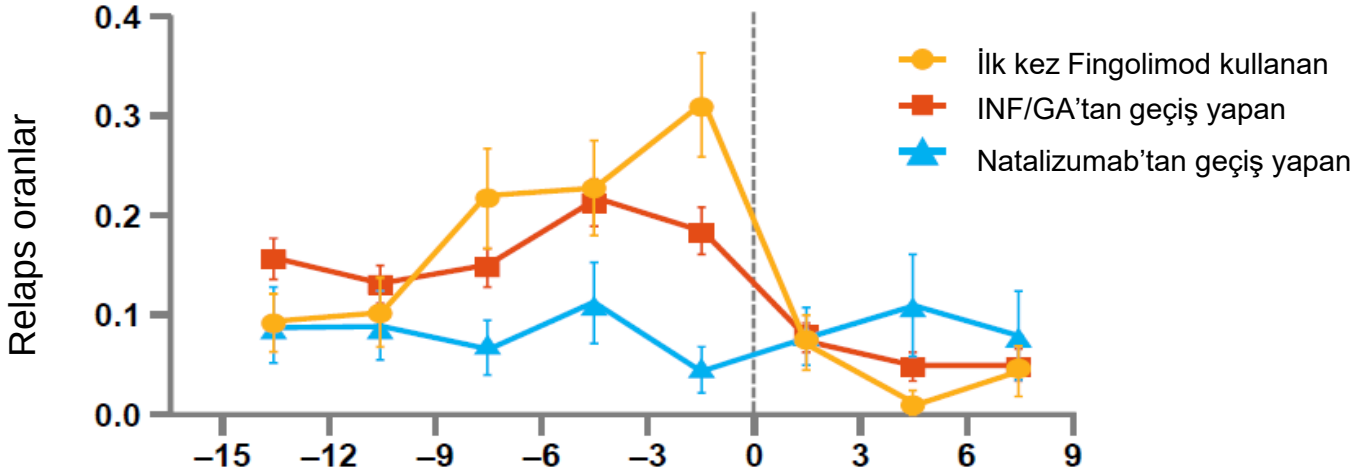


4. Yılda EDSS skoru stabil olan hasta oranı >%90

Ziemssen T, *et al.* AAN 2016; Abstract P2.072 (Poster).

1.Tedavi Geçişinde Etkinlik

MSBase Gerçek Yaşam Çalışması: INF/GA ve NTZ' dan Fingolimod'a tedavi değişimi



Fingolimoda geçen hasta sayıları

Daha önce tedavi almayan	97	97	97	97	97	97	85	70
INF/GA kullanan	350	350	350	350	350	350	269	199
Natalizumab kullanan	89	89	89	89	89	89	54	38

- **NTZ'tan fingolimoda geçiş sonrası** kısa dönemde herhangi bir rebound etki olmadan relaps oranları stabil olarak devam etmektedir.
- **INF/GA'tan fingolimoda geçiş sonrası** relaps oranları anlamlı şekilde azalmıştır.
- Fingolimoda geçişten sonraki dönemde gruplar arasında relaps oranları açısından anlamlı bir fark gözlemlenmemiştir.

Jokubaitis VG, *et al. Neurology* 2014; 82:1204–1211.

Türkiye'de Fingolimod ile yapılan çok merkezli İLK gerçek yaşam datası

9 il'de 11 Merkezden 1361 RRMS Hastası dahil edildi

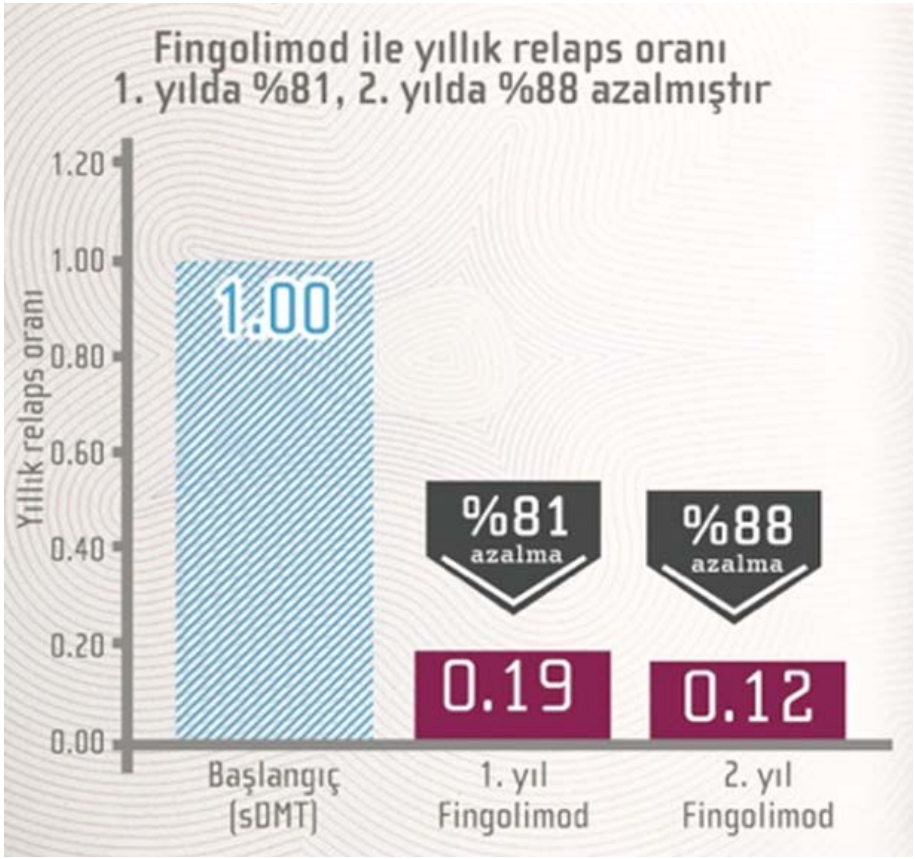
ECTRIMS 2016 'da yayınlandı.

EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

M. Terzi, M Kurtuncu, M. Eraksoy, R. Karabudak, A.Tuncer, B. Altunrende, A. Akcalı, C. Boz, S. Sevim, Y. Nur, Y. Tamam, M. Bitnel, O.F. Turan, A. Soysal, M. Ozerden, Y. Terzi real-life data from efficicacy of fingolimod treatment in multiple scklerosis patients in turkey, P651, ECTRIMS 2016

Türkiye'de Fingolimod ile yapılan çok merkezli İLK gerçek yaşam datası

Fingolimod etkili bir geçiş tedavisidir.

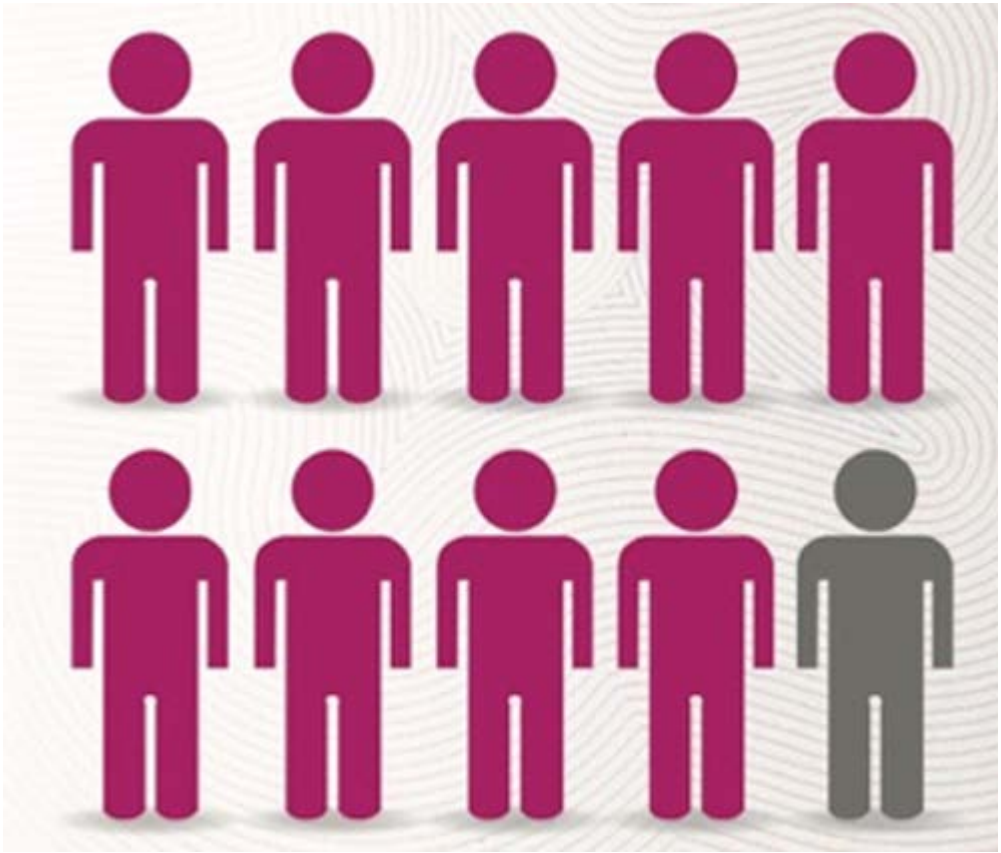


- Gerçek yaşamda Fingolimoda tedavi değişimi sonrasında klinik çalışmalar ile **tutarlı etkililik** sağlanmıştır.

M. Terzi, M Kurtuncu, M. Eraksoy, R. Karabudak, A.Tuncer, B. Altunrende, A. Akcalı, C. Boz, S. Sevim, Y. Nur, Y. Tamam, M. Bitnel, O.F. Turan, A. Soysal, M. Ozerden, Y. Terzi real-life data from efficicacy of fingolimod treatment in multiple scklerosis patients in turkey, P651, ECTRIMS 2016

Türkiye'de Fingolimod ile yapılan çok merkezli İLK gerçek yaşam datası

Fingolimod ile yaklaşık 10 hastanın 9'unda yeni MR lezyonu görülmemiştir.



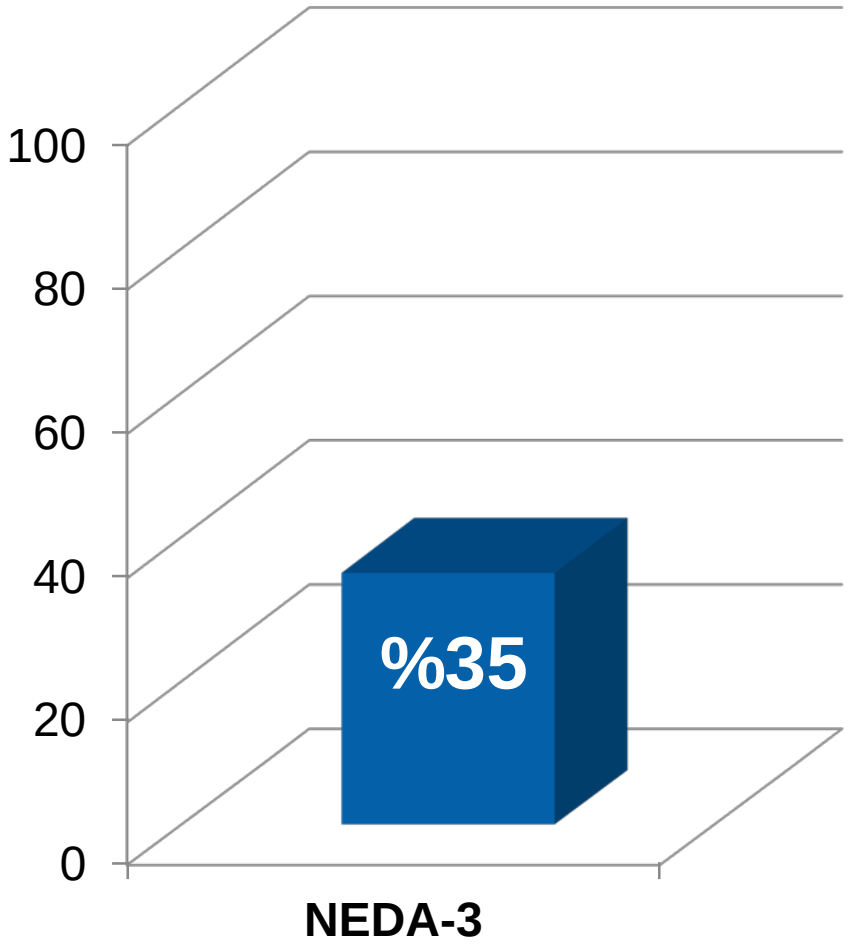
- 1. yılın sonunda yeni MR lezyonu olmayan hasta oranı **%85.9** (n:545)

M. Terzi, M Kurtuncu, M. Eraksoy, R. Karabudak, A.Tuncer, B. Altunrende, A. Akcalı, C. Boz, S. Sevim, Y. Nur, Y. Tamam, M. Bitnel, O.F. Turan, A. Soysal, M. Ozerden, Y. Terzi real-life data from efficicacy of fingolimod treatment in multiple scklerosis patients in turkey, P651, ECTRIMS 2016

Türkiye’de Fingolimod ile yapılan çok merkezli İLK gerçek yaşam datası

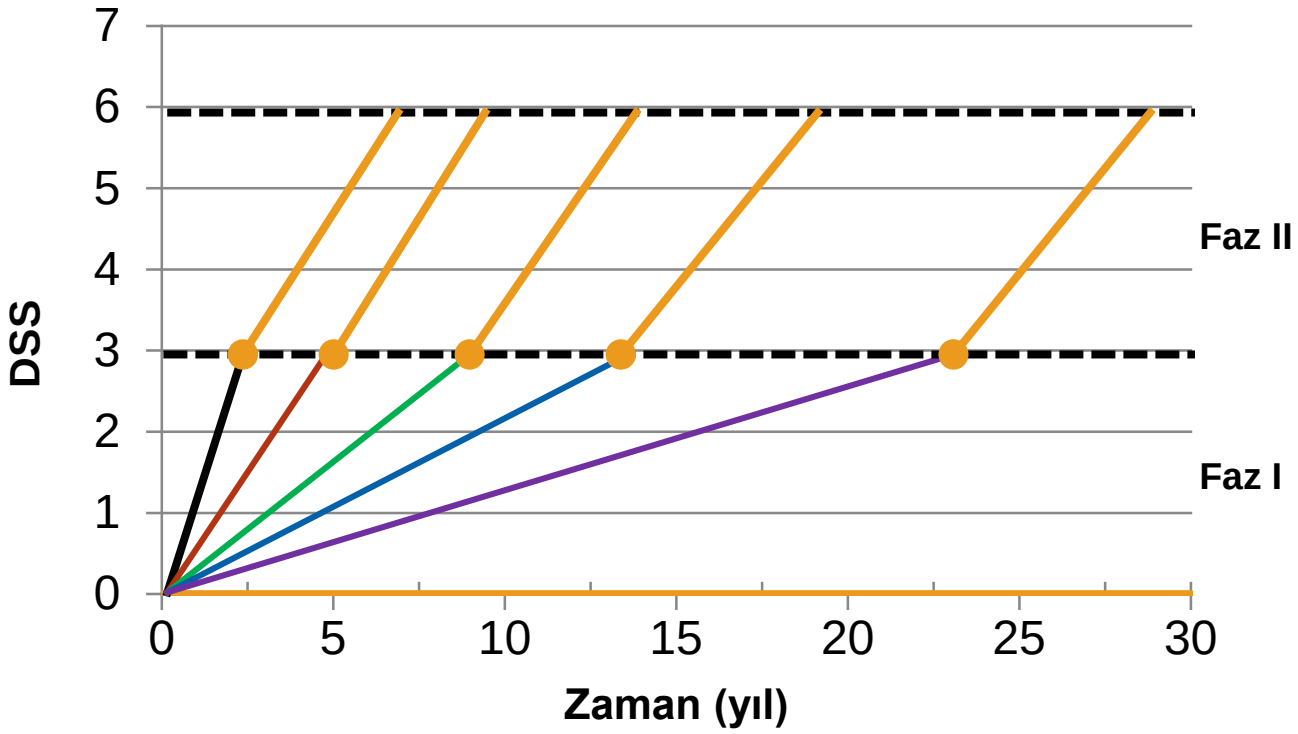
Fingolimod ile NEDA üzerinde etkinlik

- İki yıl süresince düzenli klinik ve radyolojik takibi yapılan 662 hastanın 235'inde **atak, dizabilte artışı ve MRG'de yeni lezyon gözlenmedi (%35) (NEDA 3**).



M. Terzi, M Kurtuncu, M. Eraksoy, R. Karabudak, A.Tuncer, B. Altunrende, A. Akcalı, C. Boz, S. Sevim, Y. Nur, Y. Tamam, M. Bitnel, O.F. Turan, A. Soysal, M. Ozerden, Y. Terzi real-life data from efficicacy of fingolimod treatment in multiple scklerosis patients in turkey, P651, ECTRIMS 2016

Özürlülük skoru DSS 3'ten sonra hızlıca 6'ya (sekonder progresif faza) ulaşabilir



MS'te tedavi için fırsat penceresi DSS 3'e ulaşana kadar olan zamanı kapsar

- Hastalık aktivitesi varlığında **EDSS 3'e ulaşmadan** tedavi değişimi daha faydalıdır

Leray, E., Yaouanq J. Et al. Evidence for a two-stage disability progression in multiple sclerosis Brain 2010: 133; 1900–1913 doi:10.1093/brain/awq076

Türkiye'de Fingolimod ile yapılan çok merkezli İLK gerçek yaşam datası

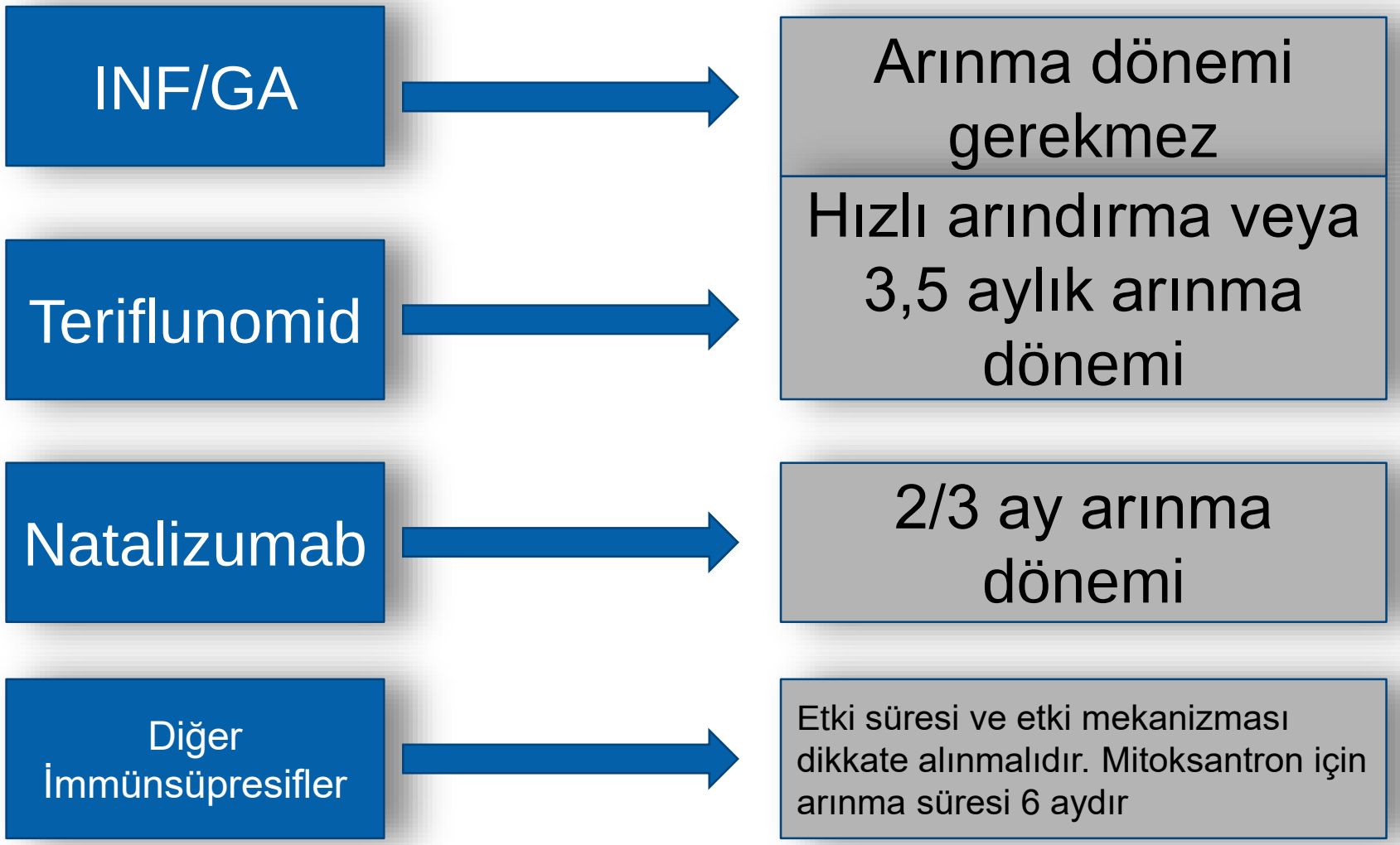
Fingolimoda geçiş sonrası özürlülük progresyonunun

- Geçiş yapıldığında **EDSS ≤ 3** olan hastalarda, Geçiş yapıldığında **EDSS > 3** olan hastalara göre daha iyi olduğu gösterilmiştir.

- Bu sonuç daha önce klinik çalışmalarda gösterilmiş olan tedavi penceresi ile ilgili **ilk** gerçek yaşam kanıtıdır.

M. Terzi, M Kurtuncu, M. Eraksoy, R. Karabudak, A.Tuncer, B. Altunrende, A. Akcalı, C. Boz, S. Sevim, Y. Nur, Y. Tamam, M. Bitnel, O.F. Turan, A. Soysal, M. Ozerden, Y. Terzi real-life data from efficicacy of fingolimod treatment in multiple scklerosis patients in turkey, P651, ECTRIMS 2016

Diğer Tedavilerden Fingolimod'a Geçiş



Gilenya Kısa Ürün Bilgisi

algoritma

- 2. basamak
- Aktif hastalarda 1. basamak

AlgoritmaTürkiye (SUT)

- Çok aktif erişkin tip RRMS hastalarında en az 1 yıl süre ile GA ,beta -İnterferon ,(DMF,Teriflunomid)tedavilerine cevap alınamayan hastalarda kullanılır

Cevap vermeyen hastalar

- 1 yıllık tedavilerle ataklarda değişiklik olmayan ,ataklarda artış gözlenen ,daha ciddi atakları olan
- Son 1 yılda tedavilere rağmen 1 atak geçiren ve KMR' da bir veya daha fazla kontrast tutan lezyon veya takip eden MR' lar da T2 lezyonlarının artması EDSS skoru 6 ve üzeri olanlarda tedavi kesilir (SUT)

Teriflunomid

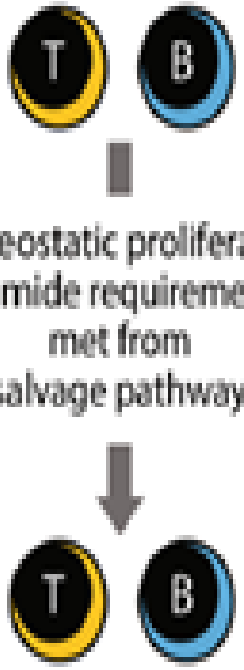
Teriflunomid'e onay

→ T.C. SAĞLIK BAKANLIĞI / THE MINISTRY OF HEALTH OF TURKEY → Ekim, 2014

→ EUROPEAN MEDICINES AGENCY SCIENCE MEDICINES HEALTH → Ağustos, 2013

→ DEPARTMENT OF HEALTH & HUMAN SERVICES • USA FDA → Eylül, 2012

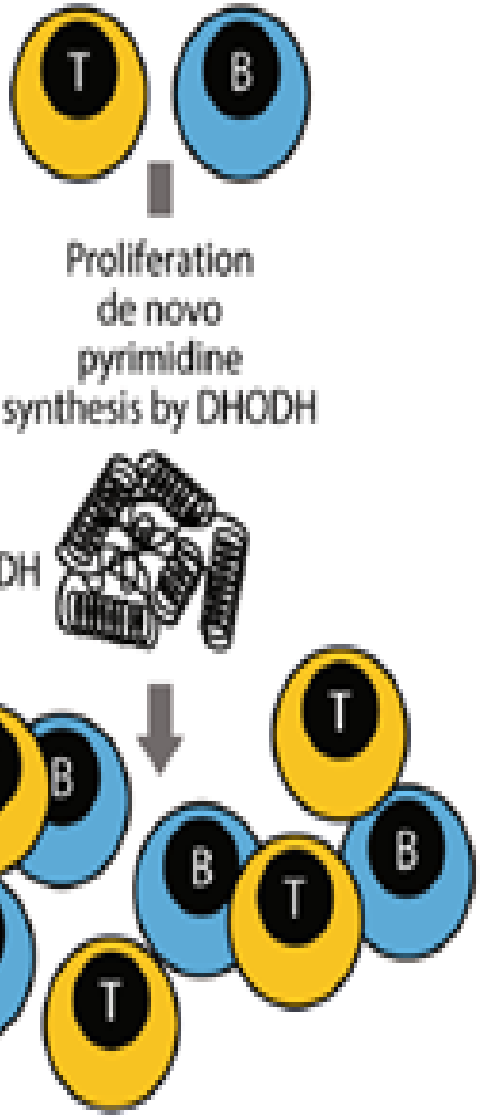
Resting lymphocytes
+/- TERIFLUNOMIDE



Homeostatic proliferation
Pyrimide requirements
met from
salvage pathway

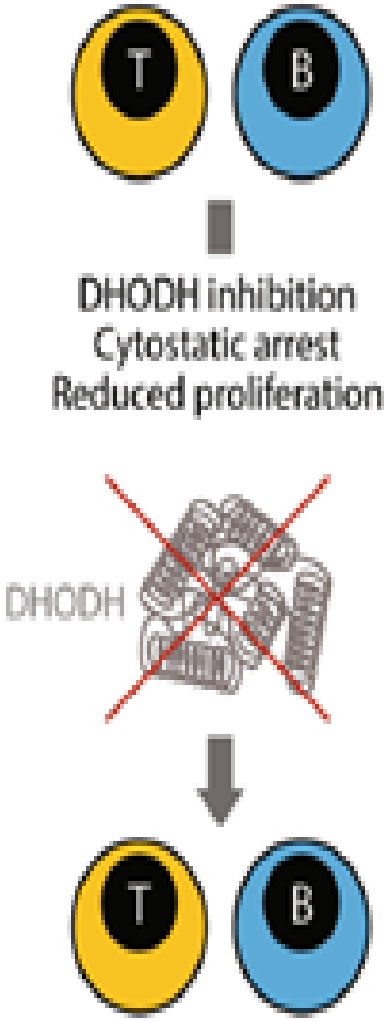
No effect from
teriflunomide

Activated lymphocytes



Proliferation
de novo
pyrimidine
synthesis by DHODH

Activated lymphocytes
+ TERIFLUNOMIDE



DHODH inhibition
Cytostatic arrest
Reduced proliferation

Teriflunomid

Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

Multiple Sclerosis Journal
18(11) 1625–1632

DOI: 10.1177/1352458512450354
msj.sagepub.com
SAGE

Pre-specified subgroup analyses of a placebo-controlled phase III trial (TEMSO) of oral teriflunomide in relapsing multiple sclerosis

Aaron E Miller[1], Paul O'Connor[2], Jerry S Wolinsky[3], Christian Confavreux[4], Ludwig Kappos[5], Tomas P Olsson[6], Philippe Truffinet[7], Lin Wang[8], Laura D'Castro[9], Giancarlo Comi[10] and Mark S Freedman[11] for the Teriflunomide Multiple Sclerosis Trial Group

TOWER

Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial

Christian Confavreux, Paul O'Connor, Giancarlo Comi, Mark S Freedman, Aaron E Miller, Tomas P Olsson, Jerry S Wolinsky, Teresa Bagulho, Jean-Luc Delhay, Deborah Dukovic, Philippe Truffinet, Ludwig Kappos, for the TOWER Trial Group†*

Summary

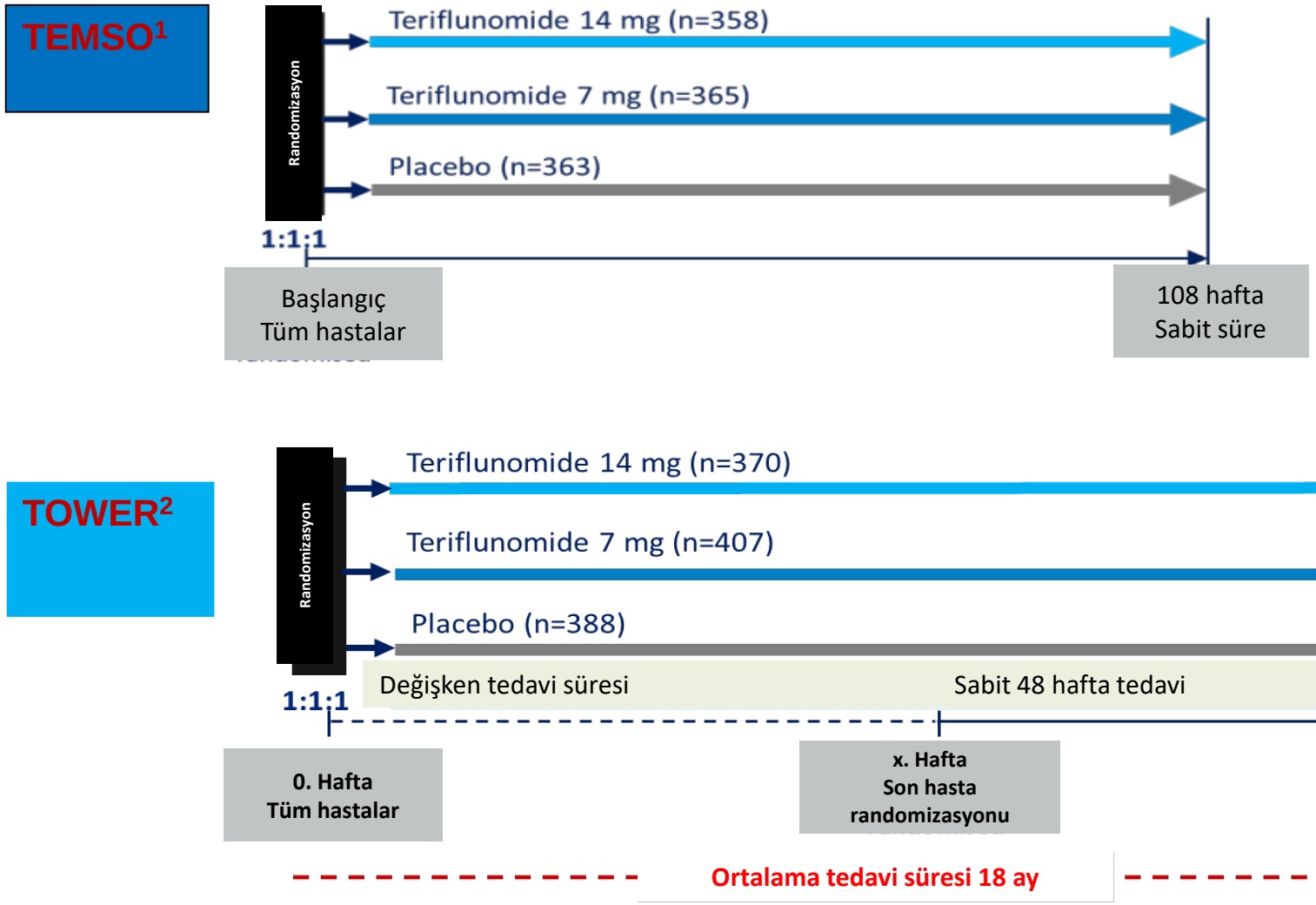
Background Teriflunomide is an oral disease-modifying therapy approved for treatment of relapsing or relapsing–remitting multiple sclerosis. We aimed to provide further evidence for the safety and efficacy of teriflunomide in patients with relapsing multiple sclerosis.

Methods This international, randomised, double-blind, placebo-controlled, phase 3 study enrolled adults aged

Lancet Neurol 2014

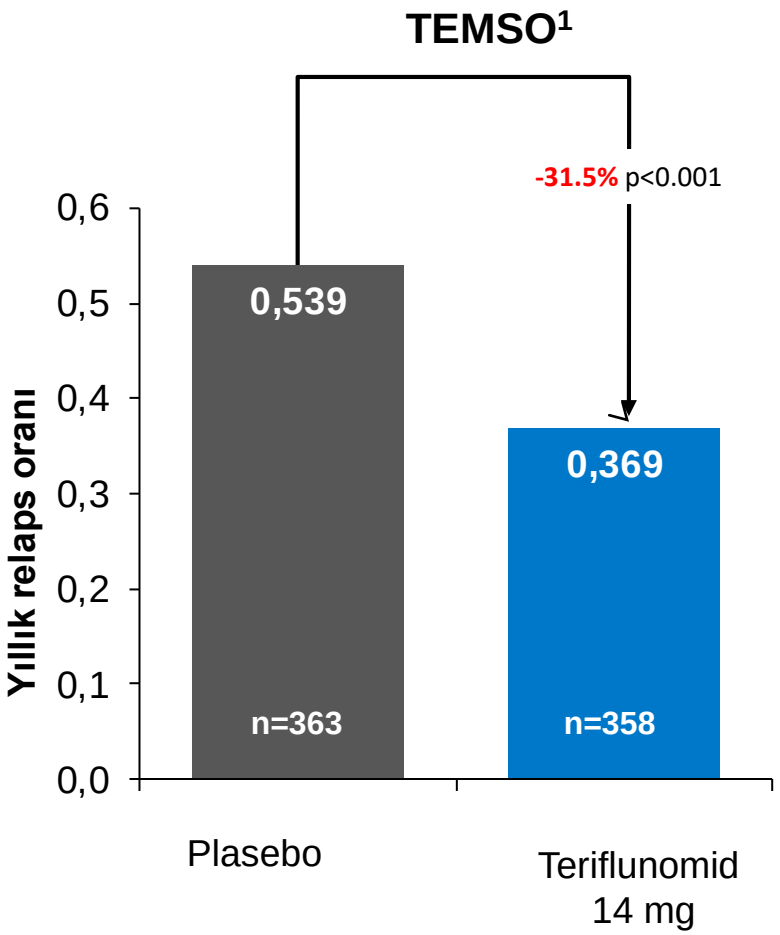
Published Online
January 23, 2014
http://dx.doi.org/10.1016/S1474-4422(13)70308-9

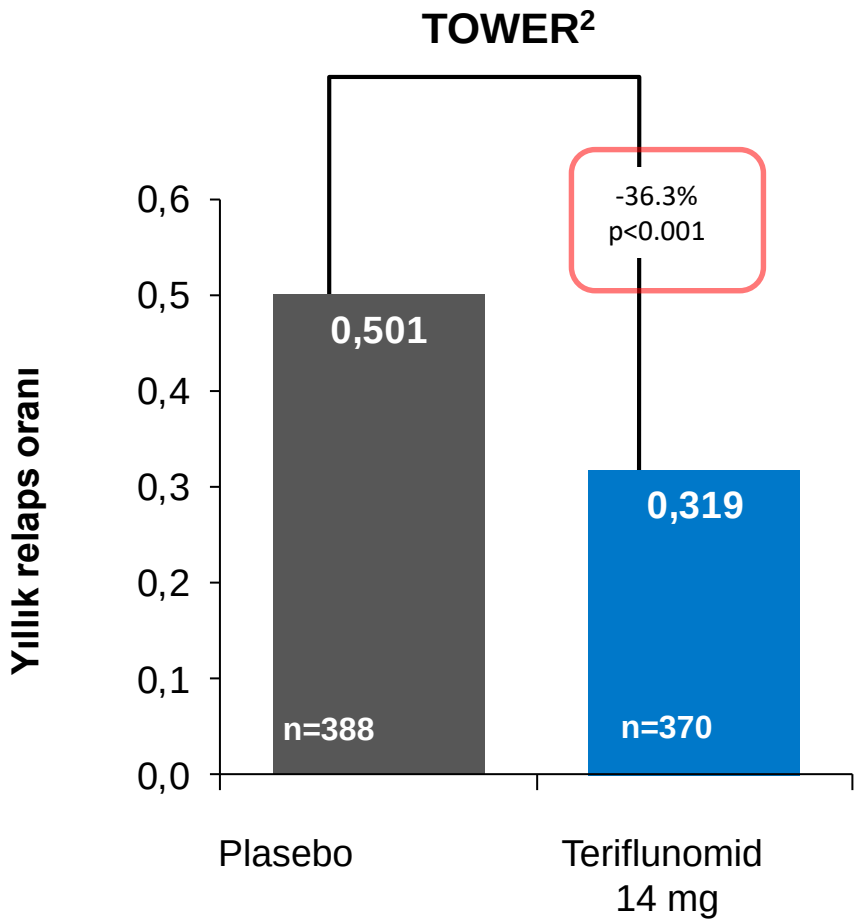
TEMSO ve TOWER Çalışma Tasarımları



1. O'Connor P et al. N Engl J Med 2011;365:1293-303, 2. Confavreux C et al. Lancet Neurol 2014 Mar;13(3):247-56).

Teriflunomid
Yıllık atak oranında anlamlı azalma





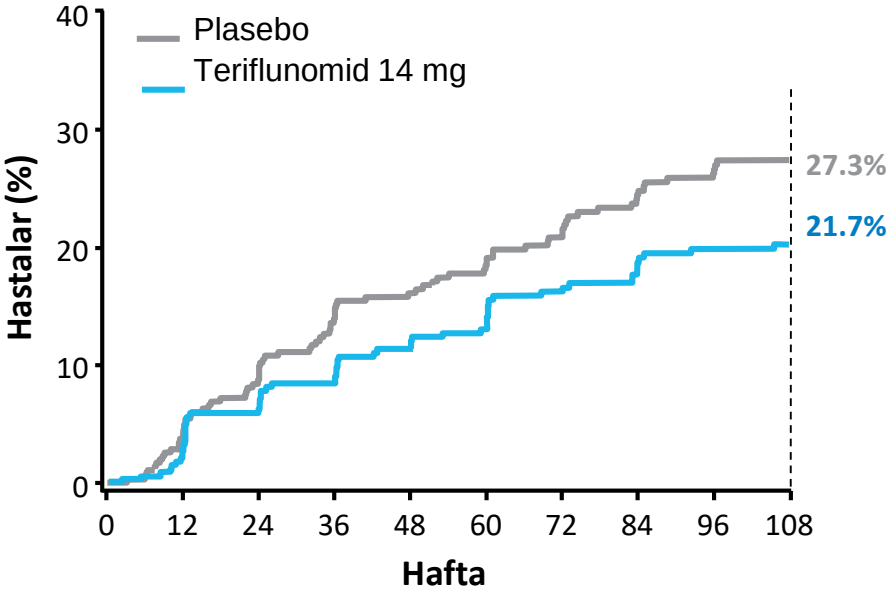
1. O'Connor P et al. N Engl J Med 2011;365:1293-303, 2. Confavreux C et al. Lancet Neurol 2014 Mar;13(3):247-56).

Teriflunomid özürlülük progresyonunda anlamlı azaltma[15, 36]

12 Hafta sürekli özürlülük progresyonu olan hastaların yüzdesi

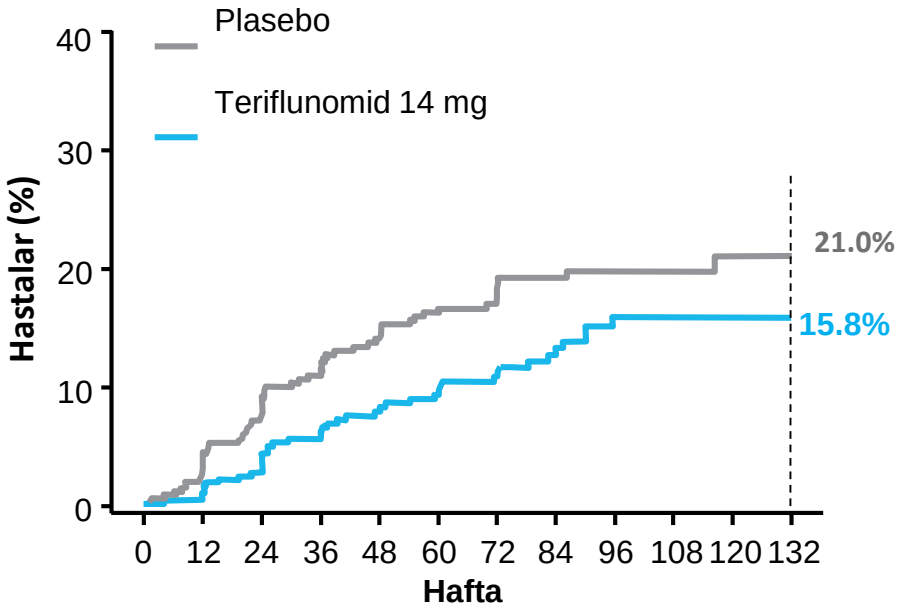
TEMSO[1]

Plaseboya göre rölatif risk azaltımı 14 mg = 29.8% (p=0.0279)



TOWER[2]

Plaseboya göre rölatif risk azaltımı 14 mg = 31.5% (p=0.0442)



1. O'Connor P et al. N Engl J Med 2011;365:1293-303, 2. Confavreux C et al. Lancet Neurol 2014 Mar;13(3):247-56).

TENERE

Research Paper

MULTIPLE SCLEROSIS JOURNAL | MSJ

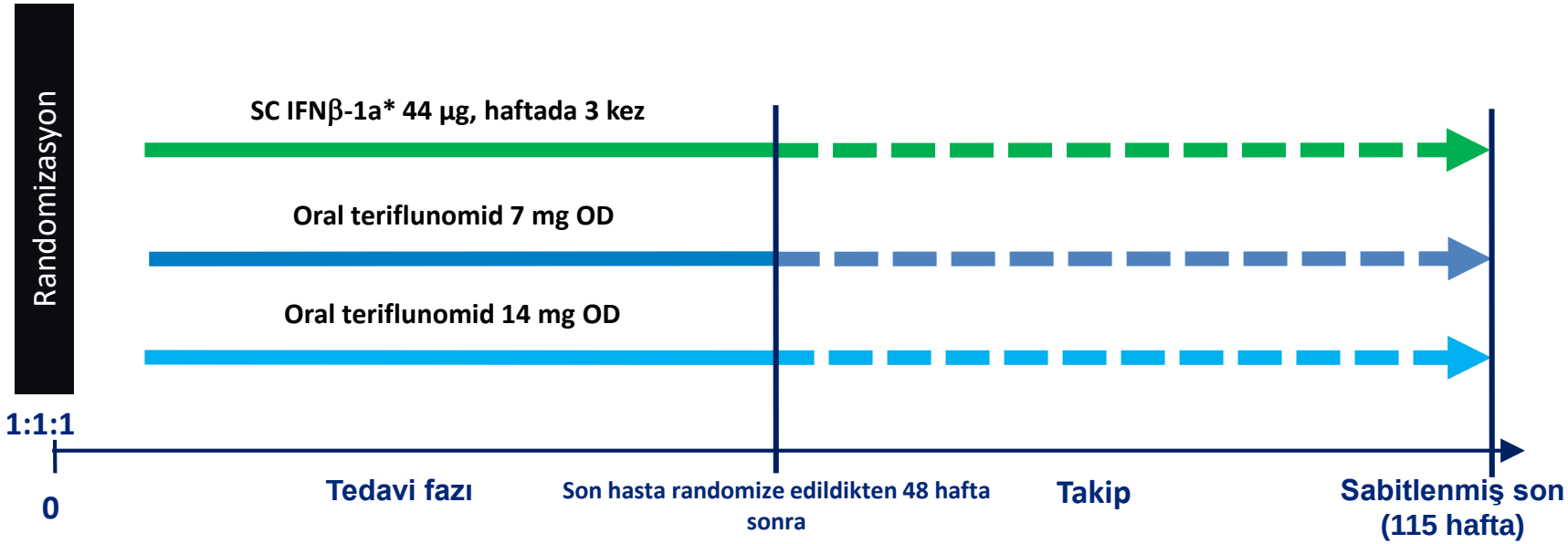
Multiple Sclerosis Journal
0(0) 1–12

DOI: 10.1177/1352458513507821
msj.sagepub.com
SAGE

Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial

Patrick Vermersch[1], Anna Czlonkowska[2], Luigi ME Grimaldi[3], †Christian Confavreux[4], Giancarlo Comi[5], Ludwig Kappos[6], Tomas P Olsson[7], Myriam Benamor[8], Deborah Bauer[9], Philippe Truffinet[8], Meg Church[10], Aaron E Miller[11], Jerry S Wolinsky[12], Mark S Freedman[13], and Paul O'Connor[14] for the TENERE Trial Group

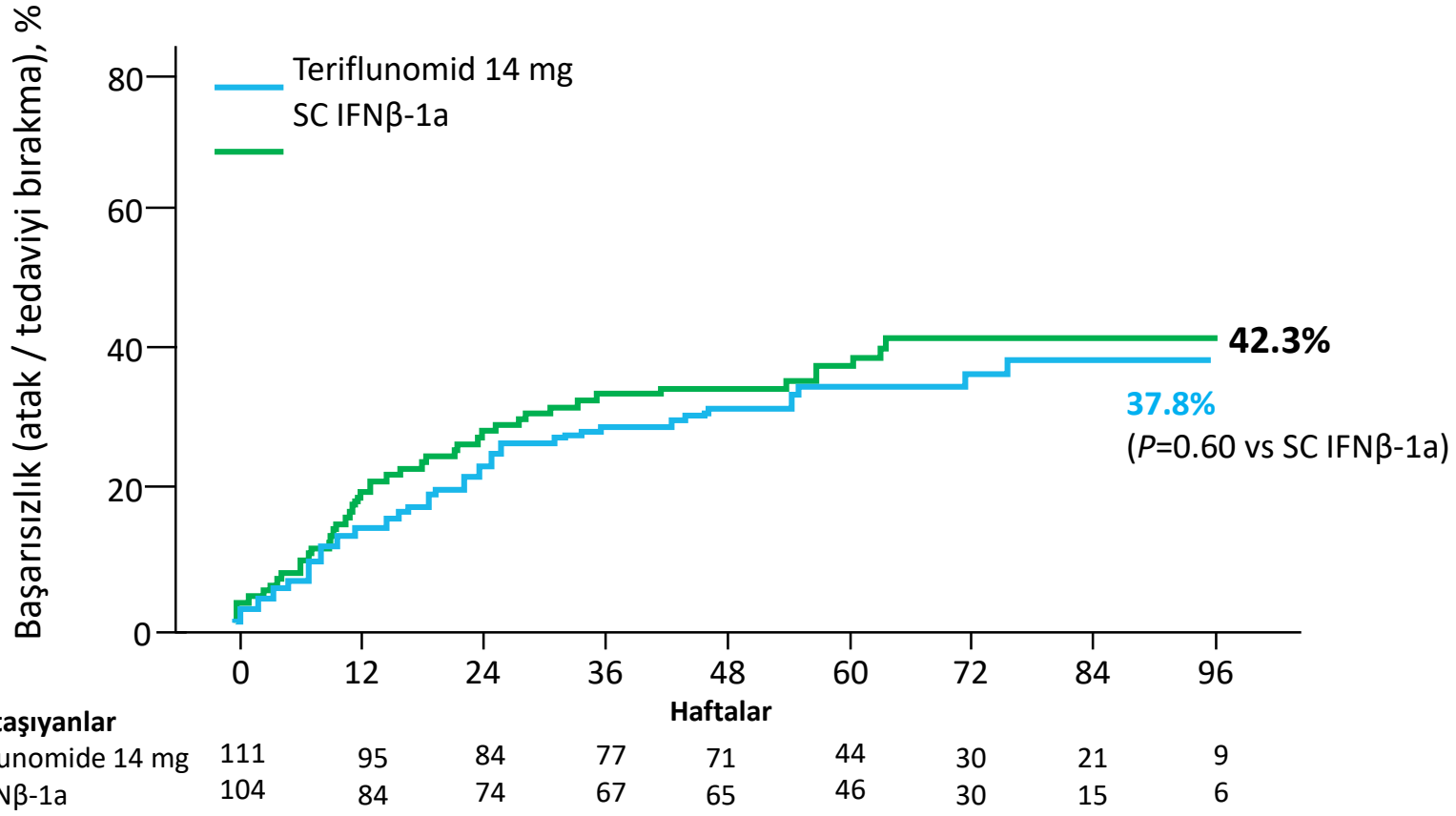
TENERE: Çalışma Tasarımı[1]



- Çok uluslu, randomize, paralel gruplu çalışma

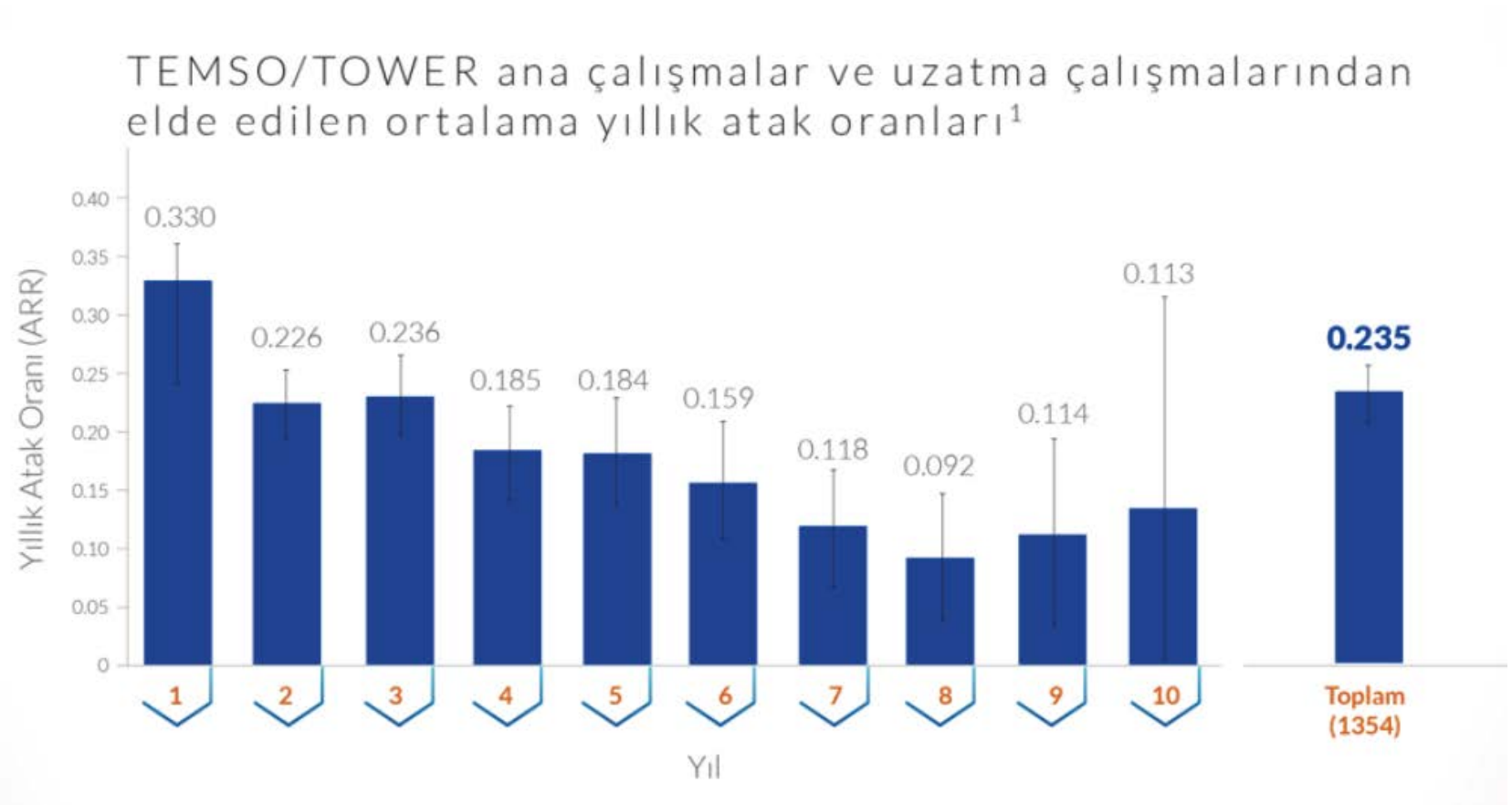
1. Vermersch P, et al. Mult Scler J. 2014 May;20(6):705-16

Başarısızlığa Kadar Zaman Üzerine Etki Teriflunomid 14 mg ve IFNβ-1a'da benzerdi [1]



1. Vermersch P, et al. Mult Scler J. 2014 May;20(6):705-16

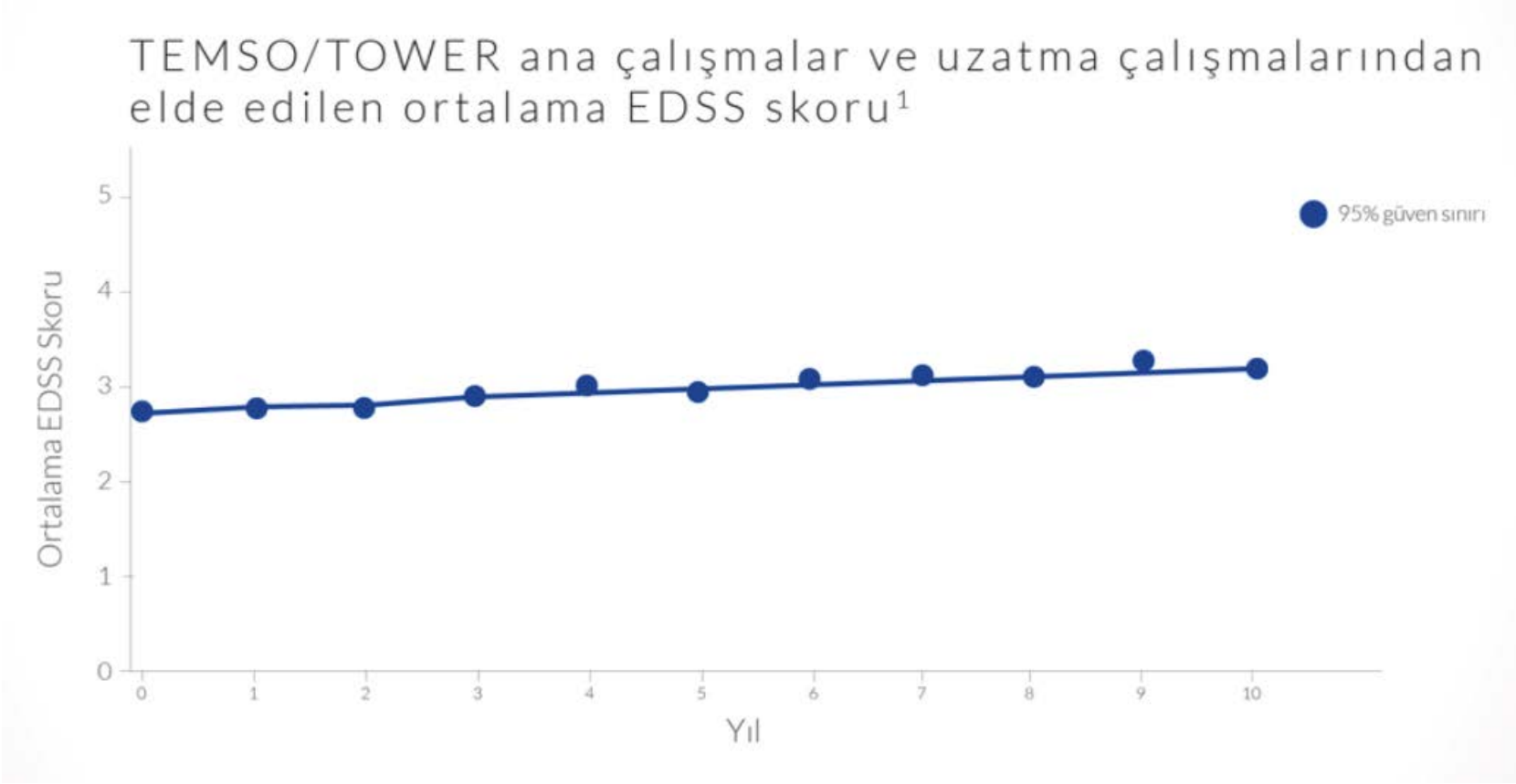
FAZ III çalışmaları ve uzun dönem takiplerinde; ARR'deki etkinlik 10 yıl boyunca devam etmiştir



10.Yıl sonunda 1354 hastanın sonuçları ITT analizi ile değerlendirilmiştir.

Oh J. Et al. AAN 2018 P391

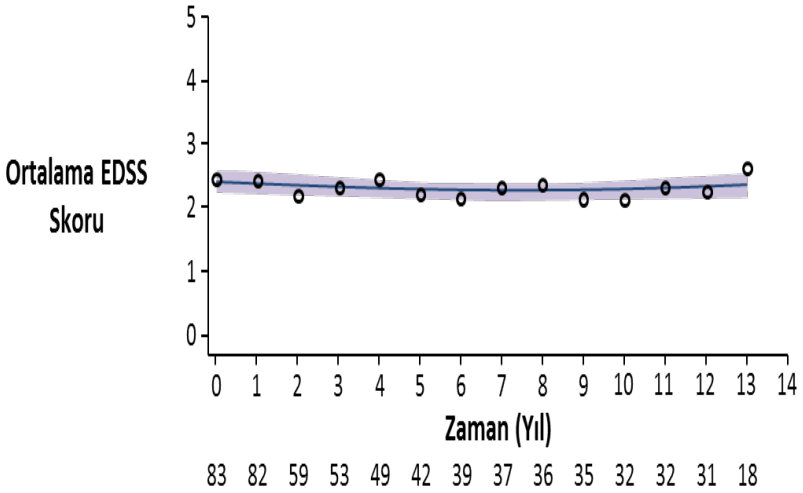
FAZ III çalışmaları ve uzun dönem takiplerinde; EDSS skoru 10 yıl boyunca stabil kalmıştır

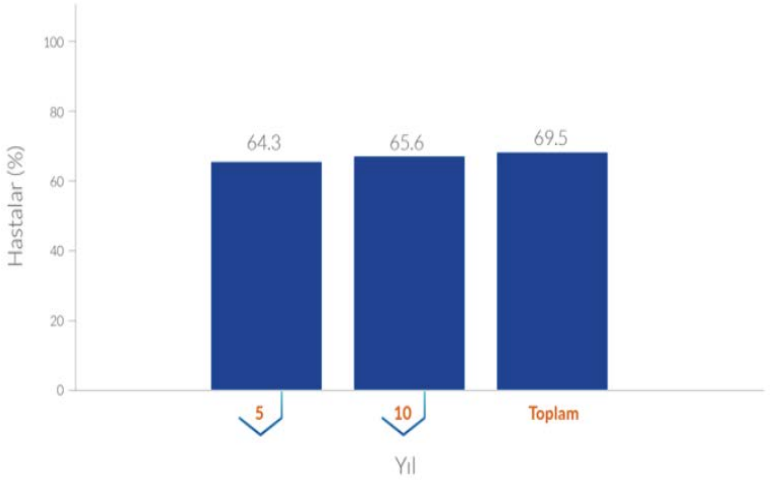


Oh J. Et al. AAN 2018 P391

Faz II çalışmasından itibaren EDSS skoru 14 yıl boyunca stabil kalmıştır

Hastaların büyük çoğunluğunda (%70'inde) EDSS stabil kalmış veya iyileşmiştir



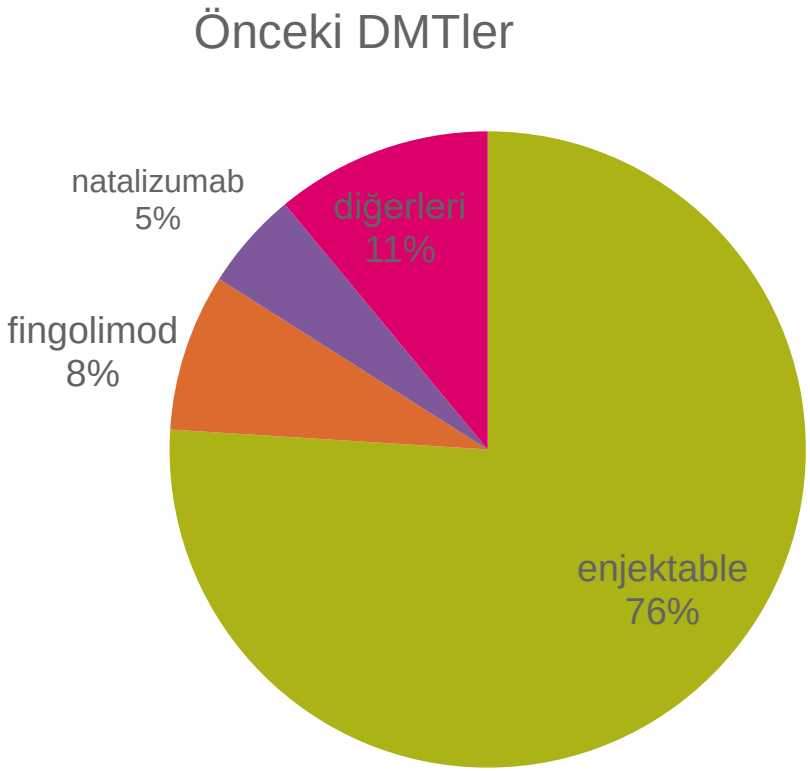


14 yıl boyunca faz II ve uzatma çalışmasına katılan hastalardaki başlangıç EDSS skoru ortalama 2.45, 5. yılda 2.21 ve 10. yılda 2.14 olarak ölçülmüştür.

Freedman SM. Et al. AAN 2018 P389

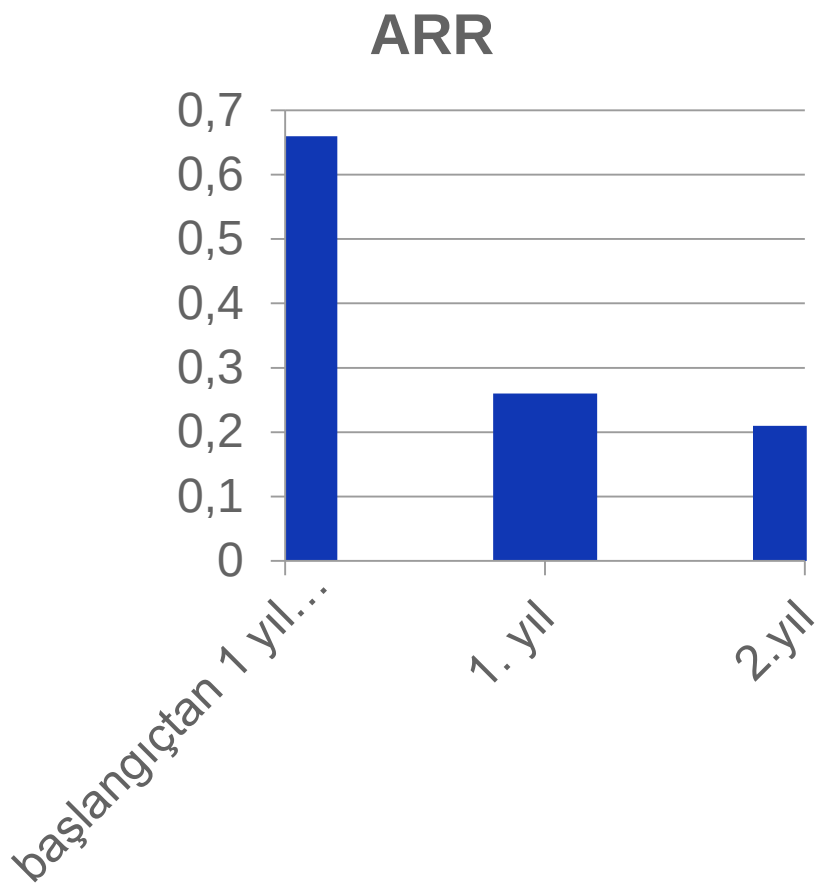
RRMS hastalarında Teriflunomid gerçek hayat deneyimi- Türkiye

Merkez sayısı	12
Hasta sayısı	532
Switch hasta saysı	372
Naif hasta sayısı	160
Ortalama yaş	40.9 ± 10.8
Tedavi öncesi yıllık atak oranı	0.66
EDSS	2,20



Boz C. Et al. ECTRIMS 2017 P679

Sonuçlar



Başlangıca göre ARR'deki azalma artarak devam etmiştir.

2. Yılın sonunda hastaların %89'u tedaviye devam etmişlerdir

- Teriflunomide Türkiye gerçek yaşam verisinin değerlendirildiği bu çalışmada yıllık atak oranlarını hem 1. yılda hem 2. yılda tedavi başlangıcına göre azaltmıştır

Boz C. Et al. ECTRIMS 2017 P679

Tedavi Geçişi

1. Aubagio Kısa Ürün Bilgisi

Algoritma

- **1.basamak hastalarda**

Kladribin

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Placebo-Controlled Trial of Oral Cladribine for Relapsing Multiple Sclerosis

Gavin Giovannoni, M.B., B.Ch., Ph.D., Giancarlo Comi, M.D., Stuart Cook, M.D., Kottil Rammohan, M.D., Peter Rieckmann, M.D., Per Soelberg Sørensen, M.D., D.M.Sc., Patrick Vermersch, M.D., Ph.D., Peter Chang, Ph.D., Anthony Hamlett, Ph.D., Bruno Musch, M.D., Ph.D., and Steven J. Greenberg, M.D., for the CLARITY Study Group*

ABSTRACT

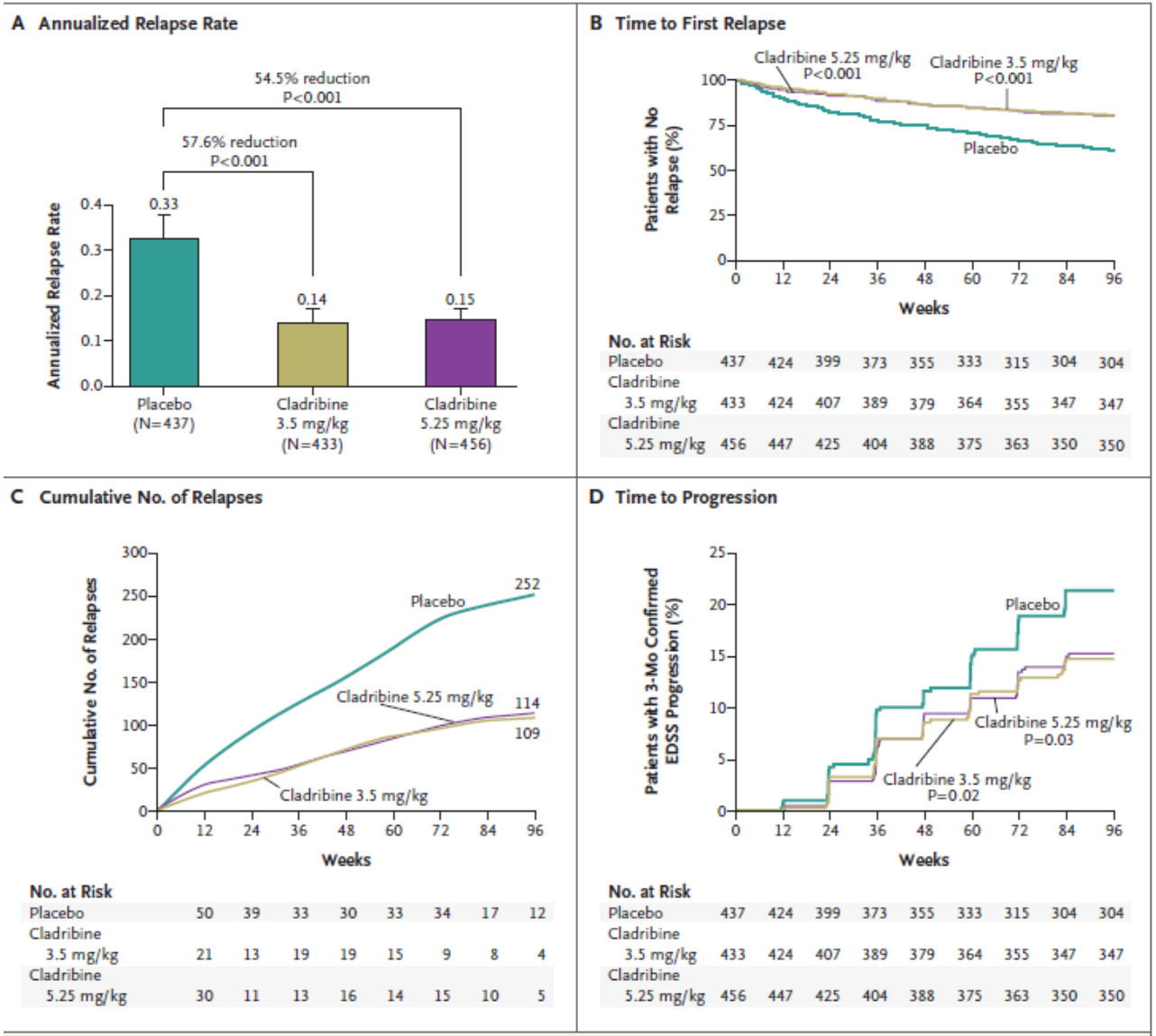
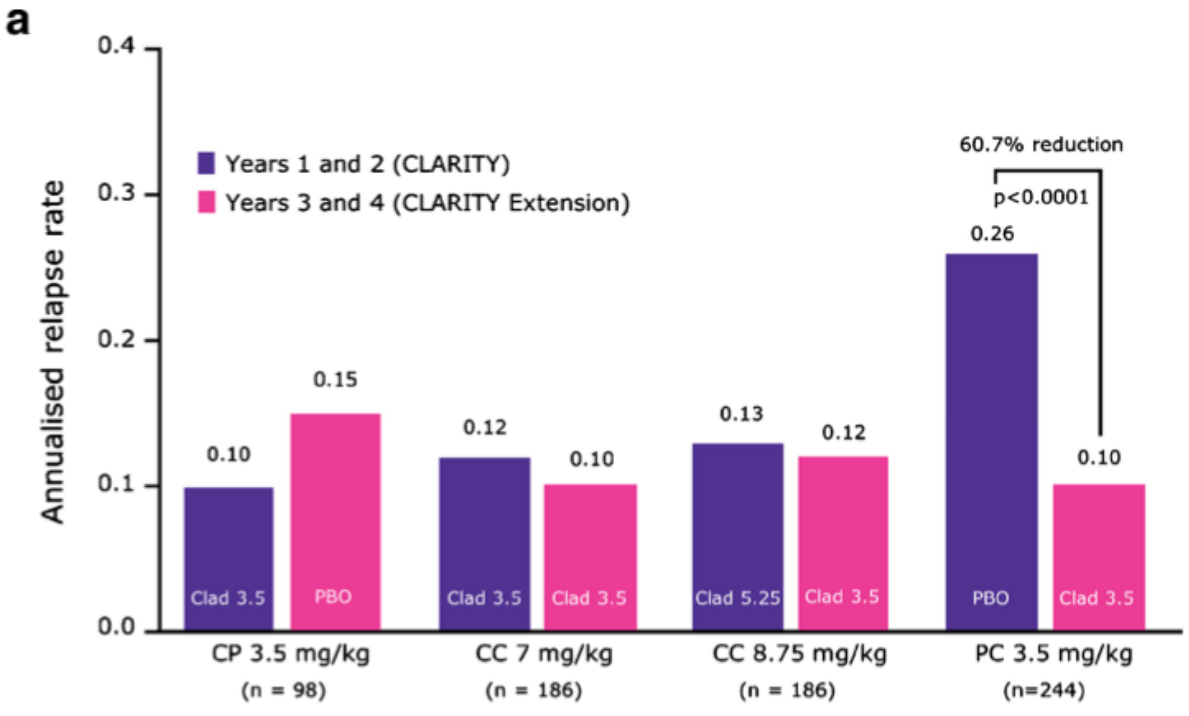


Figure 1. Efficacy Outcome Measures Relating to Relapse and Progression of Disability during the 96-Week Study Period (Intention-to-Treat Population).

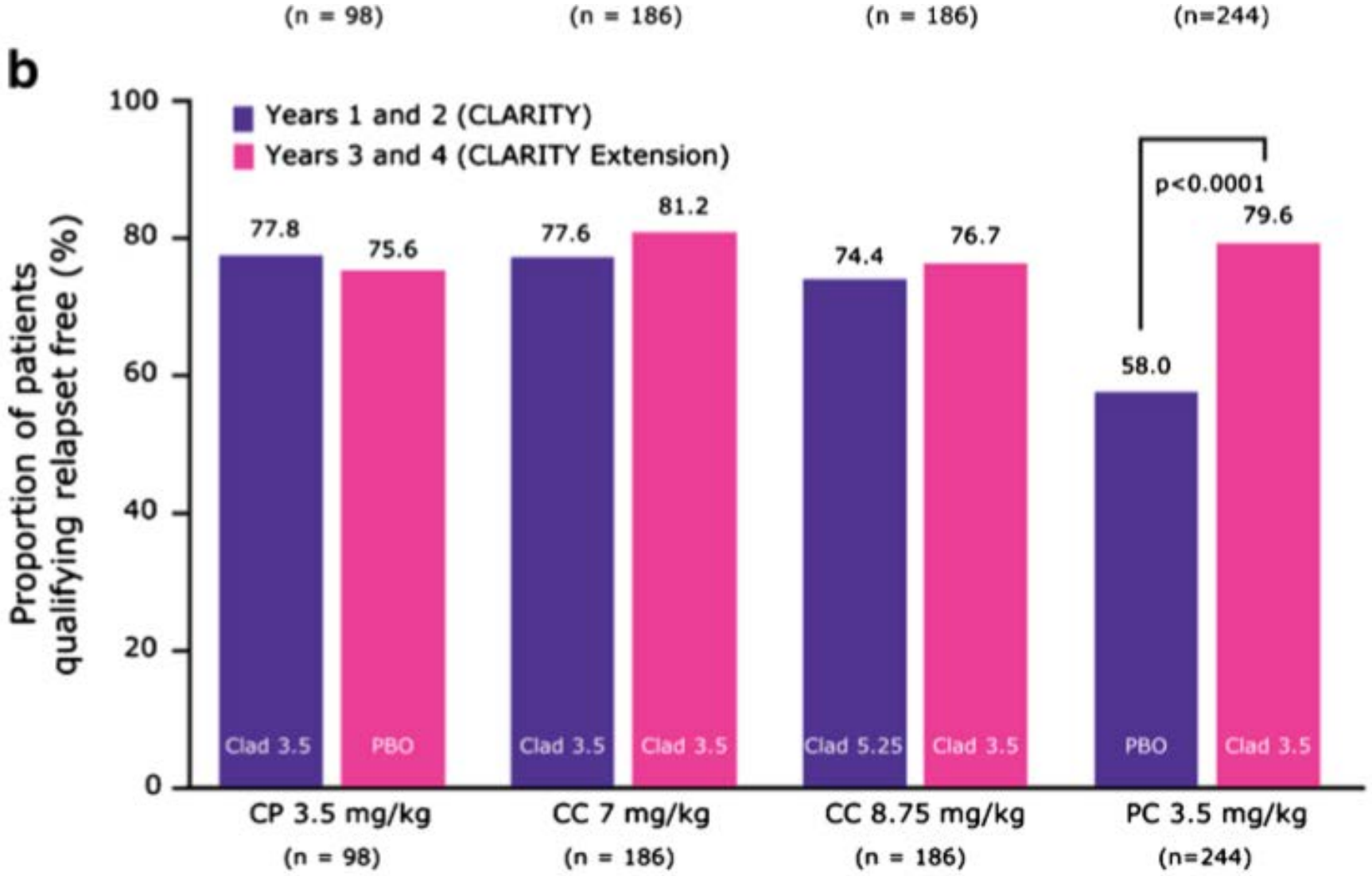
Shown are the annualized rates of relapse (Panel A), Kaplan–Meier curves of the time to the first relapse (Panel B), the cumulative number of relapses over time (Panel C), and Kaplan–Meier curves of the time to 3-month sustained progression of disability, according to scores on the Expanded Disability Status Scale (EDSS) (Panel D). In Panel A, the T bars represent 95% confidence intervals. P values that are shown in Panels B and D are for hazard ratios and 95% confidence intervals during the 96-week period, as estimated with the use of a Cox proportional-hazards model with fixed effects for study group and region.

Uzatma fazı atak oranları

Fig. 2 Effects of treatment with cladribine (Clad) tablets or placebo (PBO) on (A) annualized relapse rates and (B) proportions of patients who remained relapse free [45]
CP = Cladribine-Placebo; CC = Cladribine-Cladribine; PC = Placebo-Caldribine



Ataksız hasta oranı



- **EMA onayı aldı**
- **FDA başvurusu yapıldı**
- **Algoritma**

  2.kademede onay bekleniyor

Diğerleri (Faz II-III)

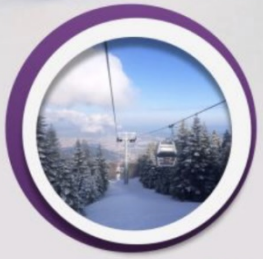
- S1P reseptör modülatörleri
  - ***Siponimod:*** S1P1 ve S1P5'e etkili:Faz II ***(BOLD)*** *(Selmaj, 2013)*
    - T2 lezyon sayısı ↓ 0,25mg grubunda <%35, 10mg grubunda %82
    - SPMS'da ***(EXPAND)*** çalışması sürüyor
  - ***Ponesimod:*** S1P1'e etkili:Faz II *(Olsson, 2014)*
    - T2 lezyon sayısı ↓ 20mg grubunda <%35, 10mg grubunda %82
    - RRMS'da ***(OPTİMUM)*** çalışması sürüyor
  - ***Ozanimod:***Faz II-III ***(RADIANCE)*** *(Cohen, 2016)*
    - T2 lezyon sayısı ↓ 0,5mg grubunda <%84, 1mg grubunda %89
    - RRMS'da IFß1b karşılaştırma çalışması ***(SUNBEAM)*** sürüyor

Diğerleri (Faz II-III)

- ***Firategrast:*** Anti -α4β-integrin molekülü
  - Faz II:900-1200mg gruplarında T1C lezyonlarında %49↓*(Miller, 2012)*
  - RRMS'da Faz III çalışması sürüyor
- ***Masitinib :*** Tirozin kinaz inhibitörü
  - PMS'da pilot çalışmada MSFC'ye etkili *(Vermersch, 2012)*
- ***İbudilast:*** Fosfodiesteraz inhibitörü
  - PMS'da Faz Iıb çalışması sürüyor ***(SPRINT-MS)***
- ***İdebenon:*** Antioksidan
  - PPMS'da Faz II çalışması sürüyor ***(IPPoMS-E)***
- ***Simvastatin:*** SPMS ***(MS-STAT)***

14. ULUDAĞ NÖROLOJİ GÜNLERİ

07 - 10 Mart 2019, Karinna Otel - Uludağ



UYKU KURSU

ANA KONULAR

- Beyin Damar Hastalıkları (Girişimsel uygulama ve tPA işlemler)
- Demiyelinizan Hastalıklar
- Başağrısı
- Yetim konular (Nörodejeneratif hastalıklarda yeni tedaviler)

www.uludagnoroloji.org

Bilimsel İletişim
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Nöroloji Anabilim Dalı – Bursa
Tel: 0.224 295 17 23
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kongre@burkon.com

- **DİKKATİNİZ İÇİN TEŞEKKÜRLER**